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POINT OF VIEW

Disagreement between guidelines regarding the third step of asthma drug therapy for school-age children

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Abstract With the help of a routine clinical case, we highlighted the difference between two of the best asthma guidelines available at the time regarding therapeutic suggestions for the so-called ''third step'' for school-age asthmatic children.

We have analyzed the scientific evidence that each of the two guidelines brings to support their position.

Finally, we have motivatedly solved the clinical scenario.

However, the question of disagreement between two guidelines remains unresolved. This can lead to unjustified differences in the management of schoolchildren with persistent asthma.
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Clinical scenario

N. is an 11-year-old boy with persistent asthma. In the last three months he had regularly taken two puffs twice a day of fluticasone 50 mg with the spacer, with excellent compliance. He says he had been fine, only once suffering breathlessness, resolved spontaneously in a few minutes. However, N. does not perform physical activity, not even moderate activity. At the objective examination some wheezing at the pulmonary listening was audible. After the physical exertion test the wheezing increased, N. had a dry cough and complained of breathlessness. Forced expiratory volume in 1 s (FEV1) was 78% at rest, reduced to 49% after exercise and increased to 94% after inhalation of salbutamol. An increase in drug therapy was considered appropriate.

The question we seek to address is: ''In school-age children with a diagnosis of asthma who are uncontrolled on low-dose inhaled corticosteroid (ICS), what is the most clinically effective second-line preventer?'' We will try to answer this with the help of asthma guidelines, as should be possible for a general practitioner.

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What do the asthma guidelines suggest?

Among the asthma guidelines with updated versions available, the British guidelines on the management of asthma (hereinafter referred to as BTS)[1] and the NICE asthma guidelines (hereinafter referred to as NICE)[2] are the ones that achieve the highest score with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) Instrument.[3]

The BTS 2019[1] suggest:

- ''In children aged five and over (5–12 years), an inhaled long-acting β2 agonist (LABA) or a leukotriene receptor antagonist (LTRA) can be considered as initial add-on therapy.''
- ''In children, options for initial add-on therapy are limited to LABA and LTRA, with evidence to support both individually, but insufficient evidence to support use of one over the other.''
- ''A systematic review of studies comparing the addition of LTRA to ICS with the addition of LABA to ICS showed that the addition of LABA to ICS was more effective at reducing asthma attacks (the primary outcome) and improving secondary outcomes including SABA use, symptoms and quality of life in adults, although differences were generally small. There was insufficient evidence on which to base conclusions regarding which add-on therapy is more effective in children.''

The mentioned systematic review (SR) is that of Chauhan Bhupendrasinh et al.[4]

Instead, the NICE 2017[2] suggest:

- ''If asthma is uncontrolled in children and young people (aged 5–16) on a pediatric low dose of ICS as maintenance therapy, consider an LTRA in addition to the ICS and review the response to treatment in 4–8 weeks.''
- ''If asthma is uncontrolled in children and young people (aged 5–16) on a pediatric low dose of ICS and an LTRA as maintenance therapy, consider stopping the LTRA and starting a LABA in combination with the ICS.''
- ''There was evidence of clinical benefit of ICS moderate dose compared to ICS + LABA for severe exacerbations but no clinical difference for lung function. The other comparisons in this age group came from a single study with 40 participants. Overall the evidence from that study suggested that ICS + LTRA and ICS low dose had a clinical benefit over ICS + LABA, particularly for severe exacerbations, quality of life and hospitalizations. However, the committee noted the very low quality of the evidence and the small sample size.''

The mentioned single study with 40 participants is that of Lenney et al.[5]

Can we now decide how to move on to the third step?

The choice, according to two of the most important guidelines on asthma,[1,2] would seem to vary between ICS/LABA and ICS/LTRA. The BTS (1) state that there is insufficient evidence to support use of one over the other. The NICE (2) most definitely indicate the association ICS/LTRA as the first choice.

This different position between these two sets of guidelines has been briefly commented by White et al.,[6] taking into account the 2016 edition of the BTS. Compared to the 2016 edition, if there are no substantial differences in the text compared to the 2019 edition, a difference is however present in Fig. 3, the one named ''Summary of management in children'': in the 2016 edition the association LTRA + ICS is not included in Fig. 3, while it is in the 2019 edition. The reference supporting both editions is the same.[4]

White et al.[6] wrote: ''Head-to-head comparisons of ICS/LABA compared with ICS/LTRA have favored ICS/LABA for effectiveness in adults (inconclusive in children). However, the cost differential is substantial between generic LTRA and LABA so when NICE used a cost-effectiveness model, the results favor LTRA, even though (as NICE acknowledges) LABA is the more effective treatment.'' These authors also point out that in pediatric age the evidence is inconclusive in order to choose between one or the other option. And that, if NICE support the choice of ICS/LTRA they do so because this choice is less expensive.

We're not satisfied, we're going a little deeper.

And we do so by examining the evidence brought to support their recommendations by the two sets of guidelines. Let's start with the BTS 2019[1] and the SR of Chauhan Bhupendrasinh et al.[4]

The authors of the SR write that: ''Of the eight trials contributing data to the main outcome, only one trial enrolled children six to 17 years of age with uncontrolled asthma given a low ICS dose.'' The pediatric study is that of Lemanske et al.,[7] whose title seems to be suitable for our question.

The authors randomly assigned 182 children (6–17 years of age), who had uncontrolled asthma while receiving 100 μg of fluticasone twice daily, to receive each of three blinded step-up therapies in random order for 16 weeks: 250 μg of fluticasone twice daily (ICS step-up), 100 μg of fluticasone plus 50 μg of a LABA twice daily (LABA step-up), or 100 μg of fluticasone twice daily plus 5 or 10 mg of a LTRA daily (LTRA step-up). A triple-crossover design and a composite of three outcomes (exacerbations, asthma-control days, and the FEV1) was used. The proportion of patients with a best response to a LABA step-up was higher than the proportion with a best response to a LTRA step-up (52% vs. 34%, $p = 0.02$) or an ICS step-up (54% vs. 32%, $p = 0.004$); the best-response results for LTRA step-up were similar to those for an ICS step-up.

In the study by Lenney et al.,[5] cited by NICE 2017,[2] the authors have included children aged 6–14 years with asthma requiring frequent short-acting beta-2 agonist relief, with symptoms of asthma resulting in nocturnal wakening and/or asthma that has interfered with usual activities in a randomized, double-blind, placebo-controlled trial with a four-week run-in period on a fluticasone propionate inhaler (100 μg twice daily). Children who remained symptomatic at the end of the run-in period were randomized into one of three double-blinded treatment regimes and were followed

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for 48 weeks. Three groups were compared: (1) inhaled fluticasone propionate 100 μg twice daily plus placebo tablet once daily; (2) inhaled fluticasone propionate 100 μg and salmeterol 50 μg twice daily (combination inhaler) plus placebo tablet once daily; and (3) inhaled fluticasone propionate 100 μg twice daily plus montelukast 5-mg tablet once daily. Unfortunately, the study was closed prematurely because of poor recruitment and the target sample size of 450 was not achieved. In total, 898 children were screened to enter the trial, 166 were registered for the four-week run-in period and 63 were randomized (group 1: 19, group 2: 23, group 3: 21), with 38 contributing data for the primary outcome analysis. There were no significant differences between groups for any of the outcomes. The authors therefore concluded that, based on their results, it is not possible to conclude whether adding salmeterol or montelukast to ICSs can reduce the number of exacerbations requiring treatment with oral corticosteroids in children with uncontrolled asthma (primary outcome).

Conclusion

Of course, we would all like to see strong, clear and numerous evidence to support all our choices. This is often not the case, but the choices for our patients must be made anyway. In the case of N. we decided to add a LABA to the low-dose ICS, our decision was influenced by the study by Lemanske et al.[7] It is only one study, but its result is clearly in favor of ICS/LABA; while the study by Lenney et al.[5] cannot reach a conclusion, as admitted by the authors themselves.

However, we believe that the main aspect of our analysis is not the final choice, this need was only a pretext. The main aspect is to have pointed out that two excellent sets of guidelines, such as the BTS 2019[1] and the NICE 2017,[2] give different suggestions on the same management aspect, as is the third step for school-age asthmatic children. We hope that they will reach a common position very soon.

For example, the authors of the GINA report 2019[8] have changed their opinion slightly. The GINA report, even if it is not possible to define a guideline, is perhaps the most widespread document on asthma in the world. In the previous version of 2018, in the figure of box 3–5 we read that for step 3 the preferred controller choice is low dose ICS/LABA, but in a note of the same box it was specified that: ''for children 6–11 years, the preferred step 3 is medium-dose ICS''. Instead, in the 2019 edition,[8] the box 3-5B, specifically dedicated to children aged 6–11 years, it is specified that the preferred controller of the third step is ''low dose ICS/LABA or medium-dose ICS''. The note has disappeared and the ICS/LABA association is in first place.

In short, even in situations where there is little evidence, a clear and decisive conclusion should be reached. Most probably, in order to achieve this, one must discuss a lot and be willing to change one's mind.

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Authors' contribution

Stefano Miceli Sopo conceived the design of the study and drafting the article. Giulia Bersani and Ester Del Vescovo acquired the data and researched the scientific literature. Mariannita Gelsomino and Stefano Miceli Sopo analyzed and commented on it. All authors revised the article and gave final approval of the version to be published.

Conflict of interests

None declared.

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