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SPECIAL ARTICLE

Are inhaled corticosteroids effective in asthma exacerbations? *Evidentia praxis*☆

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Abstract A clinical scenario is presented, from which a structured clinical question arises: In asthmatic children or adolescents with exacerbation symptoms, does the use of inhaled corticosteroids (newly instituted or base dose increased) reduce the risk of exacerbations that require systemic steroids and/or hospitalization? To answer it, we carried out a bibliographic search, with selection, evaluation and graduation of the evidence, following GRADE criteria. We did not find sufficient evidence to consider intermittent inhaled steroids as an alternative to maintenance inhaled steroids to avoid exacerbations that require the use of systemic steroids. The use of a combination of inhaled steroids with formoterol, as a rescue treatment at the onset of symptoms, is only effective when used by patients with this maintenance treatment, compared to those who only have inhaled steroids and rescue with beta2-agonists of short action; when patients already take maintenance combined therapy, combined rescue does not reduce the risk. In patients with asthma attacks attended in the emergency department, inhaled steroids compared to placebo reduce the risk of admission, but not when compared to systemic corticosteroids.

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PALABRAS CLAVE
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¿Son eficaces los corticoides inhalados en las exacerbaciones asmáticas? *Evidentia praxis*

Resumen Se presenta un escenario clínico, del que surge una pregunta clínica estructurada: ¿En niños o adolescentes asmáticos con síntomas de exacerbación, el uso de corticoides inhalados (de nueva instauración o aumento de dosis habitual) reduce el riesgo de exacerbaciones que requieran corticoides sistémicos y/o ingreso? Para contestarla realizamos una búsqueda bibliográfica, con selección, valoración y jerarquización de la evidencia, siguiendo criterios GRADE. No encontramos evidencia suficiente como para considerar los corticoides inhalados intermitentes una alternativa a los corticoides inhalados de mantenimiento para evitar exacerbaciones que requieran el uso de corticoides sistémicos. El uso de una combinación de corticoides inhalados con formoterol, como tratamiento de rescate al inicio de síntomas, sólo es eficaz cuando la usan los pacientes con dicho tratamiento de base, en comparación con los que sólo tienen corticoides inhalados y hacen rescate con beta2-agonistas de acción corta; cuando los pacientes ya toman tratamiento combinado de base, el rescate combinado no mejora el riesgo. En pacientes con crisis asmáticas atendidas en urgencias, los corticoides inhalados en comparación con placebo reducen el riesgo de ingreso, pero no si se compara con corticoides sistémicos.

Clinical scenario

Boy aged 10 years with a diagnosis of asthma treated with low-dose inhaled corticosteroids (ICSs) for the past 6 months. Under this regimen, he needed salbutamol for rescue in the context of physical activity in one isolated episode 2 months prior. The boy presents to your office after being treated in the emergency department for an exacerbation for which he received a prescription for salbutamol and oral corticosteroids. You verify that his inhaler technique is correct and that he seems to adhere properly to treatment with ICSs.

In the latest guideline of the Global Initiative for Asthma (GINA) of 2019,[1] you have read that in adolescents treated with ICSs, in the presence of symptoms indicative of worsening asthma, increasing the ICS dose to 4 times the usual is effective, but that in children with good adherence to treatment, increasing the dose to 5 times the usual is not. You have also read that in patients in maintenance treatment with ICS-formoterol, the GINA recommends increasing the dose as needed to up to a maximum of 72 μg/day of formoterol (single maintenance and reliever therapy [SMART]). It also recommends as-needed combination ICS-formoterol therapy in patients with very sporadic symptoms of asthma without maintenance therapy with ICSs and/or before physical activity in patients with exercise-induced bronchoconstriction.

The GINA advises including these recommendations in the asthma action plan provided to the patients/family. You also see that for the management of asthmatic exacerbations in children aged more than 5 years at the primary care or emergency care levels, the GINA recommends use of short-acting $beta_2$ agonists (SABAs) and systemic corticosteroids (SCSs), although in patients that do not receive SCSs, high-dose ICSs could be effective. However, neither the updated GINA strategy of 2019[2] nor the 2020 Spanish guideline (Guía Española para el Manejo del Asma [GEMA])[3] contemplate replacing SCSs by high-dose ICSs during an exacerbation, although they do contemplate maintenance of ongoing high-dose ICS therapy or its initial prescription, especially in exacerbations of moderate severity.

You decide to revise the action plan for potential future exacerbations.

Literature search and analysis of evidence

Focused clinical question (PICO strategy)

Patient
Children/adolescents with asthma (age 3—18 years; excluding studies exclusively on subjects aged >16 years or that do not present separate data for individuals under 18 years), not receiving controller therapy or in treatment with low/medium-dose ICS, alone or in combination with a long-acting $beta_2$ agonist (LABA).

a) With symptoms of acute exacerbation at home.
b) With exacerbation managed in unscheduled visit or emergency department.

Intervention

a) High-dose ICS + SABA or formoterol as needed.
b) Increased dose of ICS + SABA or formoterol.

Comparison
Placebo + SABA or formoterol as needed.

Outcome
Asthma exacerbation requiring SCS therapy and/or hospital admission.

Question: in children or adolescents with asthma that exhibit features of exacerbation, does the use of inhaled corticosteroids (newly prescribed, or with an increased dose) reduce the risk of exacerbations requiring systemic corticosteroid therapy and/or hospital admission?

Literature search

We did a literature search for randomised controlled trials (RCTs) and systematic reviews (SRs) in MEDLINE (PubMed), EMBASE, Web of Science (WoS), CENTRAL and CINAHL on February 25, 2020, without

any date or language restrictions. The initial selection of articles was made by reading the abstracts, with 2 reviewers each reading all abstracts and a third reviewer resolving any disagreement between them regarding the articles to be selected. After this initial selection, 2 reviewers read the full text of each of these articles to decide whether they would be included in the systematic review. We completed the search by reviewing the bibliography of the articles in the final selection.

The search strategy used in PubMed was: («Asthma» [MeSH] OR «Respiratory Sounds» [MeSH] OR «Bronchial Spasm» [MeSH] OR «Bronchoconstriction» [MeSH]) AND («Disease Progression» [MeSH] OR «Exacerbation» OR «acute» OR «attack» OR «Reliever therapy») AND («Administration, Inhalation» [Mesh] OR «Inhalation» OR «Inhaled» OR «nebulized» OR «SMART» OR «Single inhaler» OR «reliever therapy») AND («Steroids»[MeSH] OR «Steroids» OR «Corticosteroids» OR «formoterol») AND («child» [MeSH Terms] OR «child» OR «children» OR «adolescent» [MeSH Terms] OR «adolescent») AND (systematic[sb] OR Clinical Trial [ptyp]). For the other databases, we used an adaptation of this strategy (Appendix B of Supplemental material).

We assessed the quality of the evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE),[4] the risk of bias in RCTs with the Risk of Bias (RoB) tool of the Cochrane Collaboration, the consistency of the results, the direct relationship with the clinical scenario, the precision, the effect size, the dose-response relationship, publication bias, the control of confounding factors, the importance of the endpoint and the cost-benefit ratio.

We made tables summarizing the evidence obtained from the data retrieved from the reviewed studies. In the case of SRs that did not include separate analyses for the paediatric population, we estimated composite effect sizes, comparing 2 interventions by means of the systematic review software of the Cochrane Collaboration (Review Manager 5.3) and more than 2 interventions with the Excel-based Bayesian network meta-analysis macro NetMetaXL and WinBUGS 1.4.3. We used random effects models for paired meta-analysis and Bayesian inference with weakly informative priors.

Results

The searches yielded 627 references, excluding duplicates, out of which we selected 50 for reading of the full text, to which we added another 5 identified through the review of the references of those 50. The final qualitative review included 22 articles (Appendix B of Supplemental material). Table S1 (Appendix B of Supplemental material) summarises the characteristics and results of 5 systematic reviews[5–9] and one meta-analysis of the paediatric studies included in one of those reviews.[10] We did not summarise the findings of one narrative review[11] and one systematic review[12] because they included RCTs that we had already evaluated separately or that were included in other reviews.

Table S2 (Appendix B of Supplemental material) summarises the characteristics and results of the 16 RCTs[13–28] with information that supplemented the information obtained from SRs, either because the trial was not included in the reviews or because it provided data for specific paediatric age subgroups that was not included in the review. For 2 RCTs, we analysed the data but did not take them into account because the controls were assigned to controller therapy with ICSs as an alternative to rescue therapy with ICSs[14,28]; 2 RCTs included in the SRs made the same comparison.[19,29] Another 5 RCTs could not be included in the composite analysis of SRs because they did not analyse the primary outcomes analysed in the reviews,[16,18,26] because the sample consisted of hospitalised preschool-age children[23] or because they had a cross-sectional design[27]; the direction of effect in these studies, however, was consistent with the findings of the SR.

Table 1 presents evaluation of the quality of analysed evidence using the GRADE classification. Figs. S1–S5 and Tables S3 and S4 in Appendix B (Supplemental material) present the meta-analyses performed by our group to complete the overall analysis, which included 13 RCTs, the results of which are summarised in Table 1.

Commentary

Most reviews analyse the efficacy of ICSs, as newly prescribed treatment or in increased doses relative to the onset of exacerbation features, compared to placebo or to maintenance of the baseline dose of ICS. Two analysed the SMART approach compared to controller ICS therapy, alone or combined with a LABA.[7,10] One review analysed the efficacy of ICS as reliever medication in asthma exacerbations diagnosed at the emergency department[6] compared to placebo or systemic steroid therapy. In studies in which bronchodilators were not part of the intervention, all patients could receive SABA as needed.

The primary endpoints were usually exacerbation, defined as the need of treatment with SCSs and, in some studies, the need for emergency care or hospital admission. In analyses of the management of asthma exacerbations in the emergency setting, the primary endpoint was the need for hospital admission.

Table 1 presents evaluation of the quality of analysed evidence using the GRADE classification. It details the comparisons made in the studies and the outcome measures. All these measures were considered ''relevant'' from a clinical perspective, but not of critical importance. We found that the quality of the evidence was low or very low, save for the evidence on the comparison of ICSs versus placebo for management of asthma exacerbations in the emergency care setting and the comparison of increased-dose ICS therapy compared to maintaining the current dose of controller ICS therapy at the onset of symptoms, which was considered of moderate quality.

We could establish a theoretical hierarchy of clinical scenarios based on the baseline risk. The lowest risk would correspond to patients not taking controller treatment that start to develop symptoms, in which case we would want to know whether ICS therapy would be effective in an exacerbation. The next level would correspond to patients receiving ICSs for maintenance therapy, in who we would consider whether or not to increase the dose at the beginning of an exacerbation. The highest level would correspond to patients receiving an ICS-LABA combination for maintenance therapy, in who we would consider whether to keep using this combination or use a SABA for rescue therapy. We investigated the recommendations that would apply to these 3 scenarios to include them in the asthma action plan provided to parents.

Another scenario that we could not include in this theoretical hierarchy was the treatment of asthma exacerbations in the emergency department. Simply put, these patients have already reached the outcome that interventions in the previous scenarios attempt to prevent, regardless of the fact that their baseline risk was not the same. In this subset of patients, we could establish a particular risk hierarchy based on the compared treatments, from lower to higher steps of treatment, in increasing order, ICSs versus placebo, ICSs versus SCSs and, lastly, ICSs and SCSs versus SCSs alone. On the other hand, the interventions and outcome measures analysed in this scenario, unlike the previous scenarios, take place in the short-term. Information from these studies provides direct evidence to guide the development of protocols for management in the emergency care setting, although it could serve as indirect evidence for other scenarios.

There is evidence of low-quality that in patients with persistent asthma that are not under maintenance therapy, the use of ICSs for a week at the onset of exacerbation symptoms reduces the risk of requiring SCSs; this evidence is imprecise and indirect (preschool-age children), so estimates of the effect size based on it would be undependable. There is also evidence of moderate quality that

Table 1 **Grading of Recommendations, Assessment, Development and Evaluation (GRADE);** Evaluated intervention: inhaled corticosteroid at onset of exacerbation symptoms (rescue therapy) or in asthma exacerbations diagnosed in the emergency department/outpatient setting (detailed information provided in the Supplemental material).

Number of studies	Design	Limitations					Number of patients	Summary of results			Final quality	Relevance
		Bias	Inconsistency	Indirect relationship	Imprecision	Other		Effect				
								Baseline risk	Relative effect (95% CI)	Absolute effect (95% CI)		
Comparison: Inhaled corticosteroids vs placebo at onset of symptoms in preschool-age children												
Primary outcome: exacerbation requiring systemic corticosteroid therapy												
4[5]	RCT	−1		−1			490	43.4%	OR 0.48 (0.31−0.73)	NNT 7 (5−14)	Low	Relevant
Comparison: Inhaled corticosteroids vs placebo at onset of symptoms in school-age children												
Primary outcome: exacerbation requiring systemic corticosteroid therapy												
1[5,19]	RCT	−1			−1		145	48.6%	OR 0.57 (0.29−1.12)	–	Low	Relevant
Comparison: inhaled corticosteroids, increasing the dose (double) for rescue therapy vs maintaining the current dose in children aged 3−18 years												
Primary outcome: need of systemic corticosteroid therapy												
4[8,9]	RCT	−1					673	29.3%	OR 1.07 (0.77−1.49)	–	Moderate	Relevant
Comparison: SMART (maintenance and rescue therapy with budesonide-formoterol) vs inhaled corticosteroids for maintenance therapy and SABA (terbutaline) for rescue therapy in children aged 12−17 years with persistent asthma												
Primary outcome: severe exacerbation (hospital admission, oral corticosteroids for 3 days, emergency care)												
3[10]	RCT	−1	−1				443	23.1%	OR 0.25 (0.10−0.55)	NNT 7 (5−12)	Low	Relevant
Comparison: SMART (maintenance and rescue therapy with budesonide-formoterol) vs inhaled corticosteroids-LABA for maintenance therapy and SABA (terbutaline) for rescue therapy in children aged 12−17 years with persistent asthma												
Primary outcome: severe exacerbation (hospital admission, oral corticosteroids for 3 days, emergency care)												
4[10]	RCT	−1	−1				1393	7.7%	OR 0.60 (0.29−1.17)	–	Low	Relevant
Comparison: SMART (controller and rescue therapy with budesonide/formoterol) vs controller therapy with inhaled corticosteroids/LABA + rescue therapy with formoterol in children aged 12−17 years with persistent asthma												
Primary outcome: severe exacerbation (hospital admission, oral corticosteroids for 3 days, emergency care)												
1[10]	RCT	−2			−1		229	12.1%	OR 0.60 (0.29−1.17)	–	Very low	Relevant
Comparison: Inhaled corticosteroids vs placebo in children aged <18 years with asthma exacerbations managed in emergency department												
Primary outcome: hospital admission												
3[6]	RCT	−1			−1	+ 1[a]	240	15.2%	OR 0.19 (0.06−0.61)	NNT 9 (8−19)	Moderate	Relevant
Comparison: Inhaled vs systemic corticosteroids in children aged <18 years with asthma exacerbations managed in emergency department												
Primary outcome: hospital admission												
6[6]	RCT	−1	−1				498	25.5%	OR 0.69 (0.42−1.12)	–	Low	Relevant
Comparison: Inhaled and systemic corticosteroids vs systemic corticosteroids alone in children aged <18 years with asthma exacerbations managed in emergency department												
Primary outcome: hospital admission												
4[6]	RCT	−1	−1			−1[b]	1229	28.2%	OR 0.75 (0.57−0.99)	NNT 19 (11−493)	Very low	Relevant

CI, confidence interval; NNT, number needed to treat; OR, odds ratio; RCT, randomised controlled trial.

[a] Effect size.

[b] Publication bias.

in patients undergoing maintenance therapy with ICSs, increasing the dose to double or even 5-fold when symptoms develop does not reduce the risk of exacerbation requiring SCSs (weak recommendation against treatment). The observed effect may reflect differences in outcomes between patients that receive corticosteroids versus those that do not, without a dose-dependent effect associated to dose increases, but we do not know whether this is a short-term effect or a cumulative effect of repeated doses. On the other hand, we did not find sufficient evidence in support of intermittent ICS therapy as an alternative to maintenance ICS therapy in patients that experience exacerbations. It is worth noting that the 4 RCTs that compared these 2 regimens (2 in school-age children[14,19] and 2 in preschool-age children[28,29]) did not find significant differences, although the direction of effect supported controller ICS therapy.

There is low-quality evidence that in paediatric patients aged 12—17 years with persistent asthma, SMART (budesonide/formoterol for maintenance and rescue) compared to ICSs for controller therapy and SABA (terbutaline) for rescue reduces the risk of severe exacerbation, with 7 patients needing treatment to prevent 1 severe exacerbation. There is no evidence of SMART being better compared to ICS-LABA combination for maintenance and a SABA (terbutaline) or formoterol for rescue in this subset of patients. Although the outcomes of SMART in adults support its efficacy, the evidence available for the paediatric age group suggests that in patients receiving combination therapy, the benefits would be much smaller compared to patients receiving ICSs alone for maintenance. It should be taken into account that SMART is contemplated in patients that are already receiving combination therapy for maintenance, and thus the evidence on its efficacy would not apply to patients managed with ICS therapy alone, unless the decision is made to step up the treatment. It is also important to take into account the high cost of combination therapy compared to the use of a SABA for rescue therapy (combination therapy costs between 8 and 40 times the usual cost of SABAs). Therefore, SMART is an option to consider in patients under maintenance therapy with ICS-formoterol (weak recommendation in favour).

Last of all, there is evidence of moderate quality that in patients under 18 years that present to the emergency department with asthma exacerbations, the use of ICSs compared to placebo reduce the risk of hospital admission, with 9 patients requiring treatment to prevent 1 hospitalization. In the same scenario, ICSs have not been proven to perform better than SCSs (low-quality evidence), while there is evidence of very low quality suggesting that ICSs combined with SCSs very lightly reduce the risk of admission compared to use of SCSs alone, with 19 patients needing to be treated to avoid 1 hospitalization. It is unclear whether this evidence applies to patients that start to develop features of an exacerbation managed at the primary care level, although this could be an option in patients currently not treated with ICSs and in who SCSs have never been prescribed before, especially if the possibility of continuing treatment with ICSs as controller therapy is being considered (weak recommendation in favour).

Interestingly, although we presented the results according to the theoretical risk hierarchy, if we consider the baseline risk of control groups we do not find the expected trend, which may be explained by the fact that the greater the risk, the higher the step of treatment that control groups are receiving.

Resolution of the clinical scenario

Taking into account all the available information, we had to revise the action plan for our patient, including a personalised rescue therapy plan that would depend on the controller therapy we decided to recommend. We needed to decide whether the patient required step-up treatment with addition of an antileukotriene, increase of the ICS to a medium dose or a combination of ICS-LABA. While the patient had a recent exacerbation, resorting to a use LABA seemed unwarranted given the concerns that have been raised about the safety of these drugs in children aged less than 12 years. We also decided against adding a leukotriene due to the reports of neuropsychiatric adverse events.[30] Therefore, we tried to identify barriers to adherence and develop strategies to overcome them, or, if we concluded that adherence was not the problem, to increase ICS therapy to a medium dose.

As for the action plan in case the patient starts to develop symptoms of an exacerbation, there were two possible options: to recommend a SABA as rescue therapy or to use a combination of ICS-SABA or ICS-formoterol. From what we gathered, in patients already receiving ICS for controller therapy, increasing the dose at the onset of symptoms does not seem beneficial, although increasing the dose of ICS-formoterol in patients already using this combination for maintenance therapy, compared to patients that receive ICSs alone for controller therapy and use a SABA for rescue. A factor to consider would be the potential advantages of using a single device, which would facilitate adherence, relative to the disadvantages involved in the stepping up of treatment and its higher cost.

After interviewing the child and the family and assessing inhaler use and technique, we did not find any reason to suspect problems with adherence to controller therapy. Therefore, we decided to reinforce the controller treatment by increasing the dose of ICS to a medium dose. We also recommended continuing to use SABA for rescue therapy, scheduling a follow-up visit to reassess (if additional exacerbations or other features suggestive of poor asthma control developed in the interim) the need to step up treatment by adding a leukotriene or switching to a combination of ICS and LABA. If the latter strategy were selected, rescue therapy could consist of the same combination if formoterol had been chosen as the LABA, and otherwise of a SABA.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.anpede.2020.06.004.

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