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Are we overcoming our inability to have pediatric patients properly use inhaled corticosteroids by inappropriately escalating their therapy?

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ABSTRACT

Objective: To perform a narrative review to describe and discuss potential methods and strategies for effectively assessing and dealing with poor adherence and/or misuse of inhalers in difficult-to-treat pediatric asthmatic patients.

Data sources: Articles available in electronic databases, published from inception to April 2021.

Study selections: Relevant articles in the literature that discuss and analyze potential methods and strategies for effectively assessing and dealing with poor adherence and/or misuse of inhalers in difficult-to-treat pediatric asthmatic patients.

Results: Validated self-reported questionnaires, weighing inhaler canisters, and pharmacy records might be the most suitable methods for assessing adherence to inhaled controller therapy in clinical practice. Additionally, validated instruments could be used as an objective measurement of the adequacy of inhaler technique. Finally, empathy and a true and strong physician-parent/patient partnership have a more powerful influence on adherence than almost any other factor, and they are probably the most cost-effective methods not only for detecting poor adherence to controller therapy but also for dealing with and improving it.

Conclusions: Failure to detect or effectively handle nonadherence and/or inhaler misuse in a patient with uncontrolled asthma can mislead clinicians into thinking that the patient is nonresponsive to the original less-intensive therapy, resulting in unneeded dosage increases and/or escalation of controller therapy to more costly medications, in some cases reaching the level of biologic therapy.

Abbreviations: CPGs: clinical practice guidelines; EMDs: electronic monitoring devices; ICER: Institute for Clinical and Economic Review; ICS: inhaled corticosteroids; LMICs: low- and middle-income countries; PIAQ: Pediatric Inhaler Adherence Questionnaire; RCTs: randomized clinical trials

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Introduction

Despite important advances in our understanding of the physiopathology of asthma over the last 30 years, especially its inflammatory nature, and the availability of highly effective medications to control the disease, such as inhaled corticosteroids (ICS), many pediatric patients still fail to achieve adequate control of their asthma (1). Based on a large body of evidence from high-quality randomized clinical trials (RCTs), evidence-based clinical practice guidelines (CPGs) on asthma recommend a step-up in treatment in patients whose asthma is uncontrolled on low-dose ICS, the controller of first choice for asthma management in

pediatric patients with persistent asthma of any degree of severity (2,3). However, CPGs recommend that healthcare providers also assess adherence, inhaler technique, environmental exposure, comorbidities, and alternative diagnoses (other than asthma) (2). Nevertheless, a large body of research has shown that many healthcare providers fail to adhere to CPG treatment, fail to assess adherence to medication, fail to assess inhaler technique, and fail to discuss environmental trigger avoidance during clinical visits (4). These failures could be important contributing factors to the lack of adequate asthma control in many pediatric patients. Of these well-established problems, poor adherence and incorrect inhaler technique are two

that deserve to be analyzed in detail, because of some particularities and challenges that when not properly assessed and/or corrected could result in unnecessary and inadequate escalation of treatment. Consequently, we performed a narrative review of articles in the literature that discuss and analyze potential methods and strategies for effectively assessing and dealing with poor adherence and/or misuse of inhalers in difficult-to-treat pediatric asthmatic patients, taking into account cost-effectiveness considerations.

Methods

We conducted a narrative review of relevant articles available in electronic databases, published from inception to April 2021, that discuss and analyze potential methods and strategies for effectively assessing and dealing with poor adherence and/or misuse of inhalers in difficult-to-treat pediatric asthmatic patients.

Results

Severe asthma in children: a clinical and economic problem

Asthma is the most common chronic disease in children and is a significant and challenging public health problem worldwide, particularly in low- and middle-income countries (LMICs) (5,6). Lack of asthma control causes significant morbidity, including increased use of health services for unscheduled urgent care visits and hospitalizations, sleep disturbance, limitations of physical activity, absence from school and work, and even mortality among pediatric patients (7). In addition to the significant clinical burden, poor control of asthma is associated with an significant economic burden for the affected patients and their families, for healthcare systems, and for society as a whole, and is the cause of a significant proportion of the direct costs and almost all of the indirect and intangible costs of the disease (8).

With respect to asthma treatment, several high-quality RCTs have clearly established the efficacy of ICS, with improvement in several clinically meaningful outcomes such as asthma symptoms, need for B2-agonist medication, exercise tolerance, and unscheduled urgent care visits and hospital admissions (9). Consequently, ICS are considered to be the cornerstone of evidence-based asthma care and therefore the controller of first choice for asthma management in pediatric patients with persistent asthma of any degree of severity (2,3). Nonetheless, it is

disappointing that despite the availability of such highly effective medications in achieving asthma control, in practice, asthma is uncontrolled in a considerable proportion of pediatric patients (1).

Although many children with asthma achieve symptom control with appropriate management, a substantial subset does not (10), even with high prescribed doses of ICS. (11). Once the diagnosis of asthma has been confirmed, this poor asthma control despite high-dose ICS prescription, which is often referred to as “severe asthma”, can be divided into two categories, depending on the presence of modifiable factors or the lack thereof. One category is termed “difficult-to-treat asthma” and describes children with poor asthma control due to modifiable factors such as poor adherence to controller (i.e. inhaled) medication; inadequate inhaler technique; treatable comorbidities; exposure to secondhand smoke, visible mold, or other avoidable environmental contaminants and allergens (pets, cockroaches, etc.); inability to afford the controller therapy; family dysfunction; and psychosocial problems. Following updated evidence-based recommendations such as those provided by the National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program is also a key modifiable issue which may help to secure a substantial gain in asthma control. Briefly, these recommendations are: (1) fractional exhaled nitric oxide can be used as a possible adjunct measure but not as the sole measure for diagnosis and management of asthma; (2) methods such as multicomponent, allergen-specific mitigation interventions should be used to remove specific allergens only when there is evidence of sensitization and exposure, especially when symptoms are clearly related to exposure; (3) a short course of daily ICSs and, as needed, short-acting β -adrenergic agonists may be useful in young children (ages 0–4 years) with recurrent wheezing triggered by respiratory tract infections and no wheezing between infections when started at the onset of a respiratory tract illness; (4) although a short-acting β -adrenergic agonist as needed is still considered to be the preferred relief therapy for patients with mild persistent asthma, the combination of an ICS and formoterol as both daily controller and quick relief therapy is the recommended therapy for moderate to severe persistent asthma, steps 3 and 4, in those individuals who are at least 4 years of age; (5) a long-acting antimuscarinic agent can be added to an ICS, but a long-acting β -adrenergic agonist added to an ICS is the preferred initial step-up from ICS monotherapy in individuals ages 12 years and older; (6) a long-acting

antimuscarinic agent can be added to ICS-long-acting β -adrenergic agonist therapy, with an expected small benefit, in individuals ages 12 years and older with uncontrolled asthma, rather than continuing the same dose of ICS-long-acting β -adrenergic agonist; (7) subcutaneous allergen immunotherapy can be used as an adjunct therapy in individuals ages 5 years and older whose asthma is controlled at initiation, build up, and for maintenance phases of immunotherapy, but it should not be used in those with severe asthma (12,13).

A second category, called “severe asthma” refers to patients who, despite appropriate medication adherence, inhaler technique, and environmental trigger treatment/avoidance, experience uncontrolled asthma (11). Patients in this category require further phenotyping of their airway disease, and a bronchoscopy with bronchoalveolar lavage can be helpful in informing pathway-specific variations of the treatment (14).

Among all these potential factors that may led to uncontrolled asthma despite appropriate prescription of ICS therapy, one of the first questions that clinicians need to ask themselves is whether patients are taking this inhaled controller therapy as prescribed (15). This is because although this may seem obvious, medications work only if they are taken, and convincing evidence has repeatedly shown that the majority of parents/caregivers don’t give ICS to their children as prescribed (16), even if they report that they do (17). For this reason, the causes of poor adherence to inhaled controller medication deserve to be analyzed in detail.

Adherence to controller medication

Adherence to medications refers to the degree to which patients take the medications prescribed by their health care providers (18). Although in general suboptimal adherence to medications for treating chronic diseases is a widespread problem, inhaled controller medications for treating pediatric asthma pose an additional challenge, because of the episodic, chronic nature of asthma, with frequent periods of remission (18), the lack of immediate perceivable benefit (19), and steroid-phobia, the fear of side-effects and the consequent aversion to ICS (20), which has been widely reported in parents of asthmatic children. In addition, inhaler medication adherence may change over time, typically decreasing during the treatment period (21).

Suboptimal adherence to inhaled controller therapy is a global problem, with adherence rates fluctuating around 50%, with even lower rates in

less-affluent countries, where the asthma burden is the greatest (22,23). Suboptimal adherence to inhaled controller therapy is an issue of concern in pediatric asthma not only because of its elevated prevalence and demonstrated association with poor asthma control and the consequent increase in healthcare utilization, asthma exacerbations, and healthcare costs, but also because of its modifiable nature, with evidence showing improvement in clinically important outcomes, including the rate of asthma exacerbations, when it is improved or corrected (24). Although suboptimal adherence to medications is a very complex behavior, with many family factors contributing (25), it can be divided into two broad categories: intentional and unintentional. Although different approaches are required for dealing with these two categories (24), suboptimal adherence is likely to be caused by a combination of intentional and unintentional factors, and therefore both the intentional and non-intentional barriers to adherence must be addressed (17). Among the many barriers to adherence to inhaled controller therapy in children, some are more easily modifiable, including distracted parents with a busy lifestyle that forget to give their children medications or that have trouble incorporating medications into a daily routine (26), misunderstanding, characteristics of the treatment regimen (i.e. treatment complexity) (27), and the child’s falling asleep before the evening dose (28). Other barriers, fixed from a practical standpoint, have also been identified, such as socio-economic and demographic factors (e.g. the child’s age, maternal education, socioeconomic status, income, ethnic minority status, and poor insurance) (29,30). Finally, other modifiable barriers could be directly related to poor patient/parent-physician communication and/or relationships (usually involving short consultations with no education provided), resulting in parental misunderstanding or negative beliefs about necessary medications (typically with no or very little discussion of these problems with the healthcare provider) (4), concerns about potential side effects of medications (31), or the erroneous conception that lack of symptoms signifies lack of disease (preferring to give controller medication to their children only during symptomatic periods instead of administering regular controller therapy) (24).

A fact that greatly complicates the problem of adherence to inhaled controller therapy and asthma control is that detecting poor adherence can be a challenge, and it is in practice undetectable in routine clinical practice in many patients (32). This is because often subjective methods such as clinical judgment and

self-reporting are the only measurement of adherence we have in clinics, and it is well known that adherence is consistently overestimated when using these measurement methods (17). This is partly because parents want to be looked upon favorably by their child's physician and do not want to admit non-adherence, which leads to over-reporting the true level of adherence (a behavior known as social desirability bias) (17), but also because of inaccurate recall (33). For this reason, an essential and necessary first step when evaluating a patient with uncontrolled asthma despite appropriate prescription of inhaled controller therapy is to use an adequate and reliable method of assessment of adherence. This will allow clinicians to more accurately determine whether uncontrolled asthma symptoms are due to a failure to follow prescribed recommendations, inadequacy of treatment, or true resistance to standard asthma treatments (34).

Failure to detect nonadherence to inhaled controller therapy, typically ICS, in a patient with uncontrolled asthma can mislead clinicians into thinking that the patient is non-responsive to the original therapy, resulting in unnecessary requests for expensive diagnostic tests in order to try to understand the patient's poor response to treatment (17). Likewise, failure to detect nonadherence usually results in unneeded dose increases and/or escalation of controller therapy to more costly medications (35), in some cases reaching the level of biologic therapy. Accurate indication for these more intensive and more costly medications, including biologics, requires, among other things, the demonstration of an adequate level of adherence to the original, less intensive and less costly therapy (36). For the above-mentioned reasons, although there are many ways of assessing adherence, each with varying degrees of objectivity and validity (Table 1), it is of utmost importance to ensure an assessment of adherence to inhaled controller therapy as accurately and objectively as possible (18). Among all available objective methods, electronic monitoring devices (EMDs) are considered to be the most objective and the best currently available method for assessing adherence to inhaled controller therapy (34). However, despite their great potential, because of their high cost and low availability they are still not used in routine clinical practice; furthermore, the economic case for this monitoring has not yet been established. Therefore, considering the advantages, disadvantages, and feasibility issues of all available methods for assessing adherence to inhaled controlled therapy (Table 1), validated self-reported questionnaires, weighing inhaler canisters, and pharmacy records could be the

most suitable methods for assessing adherence to inhaled controller therapy in clinical practice, especially in difficult-to-treat asthmatic patients. Much of the information in the table is self-explanatory, but a few aspects need to be noted. First, although subjective methods such as self-reported validated questionnaires are less accurate than more objective methods (e.g. EMDs or canister weighing), they could be a useful starting point that could provide a reasonable picture of patients' adherence (37), especially if they meet two conditions. The first is the inclusion of an empathic and non-judgmental introduction to the questionnaire that acknowledges the likelihood of poor adherence and encourages parents to report these behaviors or attitudes candidly (38). The second is the completion of a validation process with objective methods that demonstrate adequate internal consistency and test-retest reliability, among other psychometric properties (18). In addition, ideally these questionnaires should include questions or items that assess daily patterns of use with each regularly prescribed medication and that help to clarify and interpret patterns of medication use (including questions or items that assess the patient's criteria for adequate or appropriate adherence and the reasons for low or erratic compliance, including physical, psychological, social, or financial barriers) (18,39). One questionnaire that meets most of the above-mentioned requirements is the Pediatric Inhaler Adherence Questionnaire (PIAQ) (40). The PIAQ contains six questions based on the literature, on focus-group discussions, and on the researchers' professional experience, preceded by an introduction that acknowledges the likelihood of poor adherence and encourages parents to be honest and sincere in their answers. Additionally, the questionnaire explores reasons for low or erratic compliance, and when validated against the weight of inhaler canisters as an objective gold standard, showed adequate concurrent criterion validity (i.e. the degree to which the measurement correlates with some other measure of the specific construct of inhaler adherence) and test-retest reliability (i.e. the consistency of the questionnaire results measured on 2 occasions with no change in adherence level between them). Consequently, the PIAQ is a valid, reliable, quick, inexpensive, and easy-to-use instrument that allows quantitative assessment of inhaled controller therapy in children with asthma and may be useful across a range of clinical settings, especially those where it is not feasible to use EMDs (40). Other questionnaires used for measuring adherence to controller therapy are the Morisky scale (41) and the Medication Adherence Report Scale (42).

Table 1. Key methods for measuring adherence to inhaled controller therapy.

	Description	Advantages	Disadvantages	Feasibility issues
Healthcare provider assessment of adherence	Judgment by healthcare provider of patients' adherence level	- Fast, low-cost, easy to assess	- Subjective method - Highly variable degree of accuracy, usually overestimating adherence.	Low cost
	Validated self-reported adherence questionnaires	- Fast, low-cost, and simple-to-administer method - This method can provide detailed information about patterns of inhalers use, patients'/parents' perception of appropriate use, reasons for poor adherence, and barriers to medication use - Accuracy may be increased if questionnaires include an empathic and non-judgmental introduction to the questionnaire that acknowledges the likelihood of poor adherence and encourages parents to report these behaviors or attitudes candidly	- Subjective method - Limited by the patient's memory, and it has a highly variable degree of accuracy. - Adherence to inhaled controller therapy is frequently overestimated when compared to objective measures.	Low cost
Weight of inhaler canisters	Using this method, by determining the weight of the controller inhaler at the beginning of the measurement period using a digital scale, the weight of each discharge of the inhaler, and the weight of the inhaler at the end of the measurement period when the inhaler/canister is returned to the healthcare provider/researcher, it is possible to calculate how much of the medication has been taken	- Objective method - This method can be used as an additional way of obtaining an objective validation of self-reporting and/or asthma diaries	- Allows calculating how much of the medication has been actuated, not necessarily inhaled - Dose dumping and use of the inhaler by a third party could produce inaccurate adherence measurement results - Provides no information about daily patterns of medication use or reasons for poor adherence - Dependent on the patient's returning all indicated inhaler/canisters	Low to moderate cost (it is necessary to include the cost of a digital scale and the staff time in the calculation of the costs of the method)
Prescription refill rate	Examination of pharmacy records on the amount of medication dispensed from a pharmacy	- Objective method - Relatively easy to obtain - This method can be used as an additional way of obtaining an objective validation of self-reporting and/or asthma diaries	- Limited utility if health information data are not available, are difficult to obtain, or are of poor quality - Provides no information about daily patterns of medication use or reasons for poor adherence - Allows calculating how much of the medication has been dispensed, not necessarily inhaled	Low to moderate cost
Electronic monitoring devices	Measurement of when and how often patients (parents) activate the inhaler.	- Objective method - Current gold standard for measuring adherence - Newer devices permit checking inhaler technique in addition to adherence - Calculation of adherence with some of these devices is not affected by dose dumping	- Method not currently available for routine clinical use in many countries. - These devices do not provide information on why patients are nonadherent - These devices are not available for all types of inhalers	High cost, low availability

Second, although pharmacy records may be an acceptable option for assessing adherence to inhaled controller therapy, in a number of countries this is not a feasible option, because health information data may not be available, may be difficult to obtain, or may be of poor quality (43).

Third, although it is possible that weighing inhaler canisters would not be a feasible option for use in all patients, it could be a feasible and valid option in some difficult-to-treat asthmatics, such as those attending a severe-asthma clinic. However, it is worth mentioning that some inhalation devices have dosage counters, and therefore there is no need to weigh them.

Finally, the methods could be used in conjunction, in order to make the most of the main advantages of each (i.e. the objectivity of the weighing inhaler canisters and the possibility of obtaining detailed information about patterns of inhalers use, patients'/parents' perception of appropriate use, reasons for poor adherence, and barriers to medication use when using self-validated questionnaires) (18).

Although determining whether a patient is adherent does not automatically lead to improved adherence (39), it is usually an essential first step for targeting adherence behavior effectively. Therefore, we cannot overemphasize the critical importance of empathy and a true and strong physician-parent/patient partnership, which could help identify non-adherent patients and increase the level of adherence to taking inhaled controller therapy (44). Consultations by an arrogant, autocratic, or simply busy physician with time constraints who attempts to force treatments, does not provide enough information, or fails to discuss the parents'/patients' perceptions or concerns about the disease and/or its therapy, and that end without mutual agreement, more often result in poor adherence, with parents administering controller therapy only if their children are symptomatic, or not giving it at all (45). This is because there is evidence showing that differences in perspectives between asthmatic patients/parents and physicians of what is best for the patient and what the patient perceives that he or she needs could affect the patient's behavior and ultimately affect adherence to the prescribed therapy. The parental decision to follow the physician's recommendations for their children largely depends on their own feelings and perceptions about asthma and the prescribed medication use, by balancing the severity of the disease with the vulnerability of their children, as well as the perceived necessity or added benefit of therapy against the real or perceived danger or disadvantages of the prescribed medications (including side effects) (46,47). This necessity-concern framework has been

shown to explain medication adherence in several chronic diseases, including asthma (48). It is important to recognize that what seems commonplace to physicians can be foreign to the children/parents (49). If this fact is not recognized and/or addressed, it will indeed affect adherence to the prescription. In the same manner, there is also evidence showing that parental perceptions about illness and medication can be modified by health care providers during close and intensive follow-up (50). Likewise, better understanding of the perspective of the patient can improve asthma control, because it could reinforce behavior that improves adherence to the medication and ultimately achieve asthma control. To better understand what children with asthma and their parents or caregivers desire in the way of support from their physician providers, Rubin et al. conducted a survey of nearly 1000 parents of asthmatics affiliated with the Asthma and Allergy Network (49). It is worth mentioning that several reported aspects of this study, such as eye contact, carefulness and completeness of assessments, attention paid to the patient, a partnership in developing care plans, increased listening and interaction on the part of the physician, concerns about side effects of the medication, doubts about the asthma diagnosis, and recognition of the patient's perceived needs, are susceptible to being improved by enhancing empathy within the healthcare provider-patient relationship, thus improving the outcome of asthma control (49). Likewise, the fact that many asthma patients and caregivers want to be more involved in the treatment but a large proportion of the caregivers don't feel that their child's healthcare provider sufficiently involves them during clinic visits (4) is also susceptible to improvement by enhancing empathy within the healthcare provider-patient relationship. Non-judgmental, empathic healthcare provider-patient communication may assist in understanding the child's/parent's perceptions of the illness and its treatment and in understanding their perspective, capacities, and resources for adhering to treatment. This understanding may help in developing a type of contract with the physician that will achieve a specific goal and in adopting a better approach to the development of effective educational and motivational strategies aimed at effectively targeting adherence behavior (24). Consequently, shared decision-making and open-ended questions about parents'/patients' perceptions or concerns about the disease and/or its therapy should be the cornerstone of clinic visits. Additionally, as mentioned above, other barriers to adherence, such as forgetfulness, out-of-pocket drug costs, and treatment complexity could also be responsible for suboptimal adherence.

These modifiable barriers could be more easily addressed merely with reminders or by promoting regular habits (e.g. taking the medication before cleaning the teeth or at the same time every day), using a low-cost treatment, and simplifying treatment regimens (e.g. reducing the number of inhalers and doses per day) (24). With regard to the latter aspect, our group demonstrated that compared with twice-daily dosing, once-daily ICS dosing for treating pediatric patients with persistent asthma is associated with greater effectiveness in asthma treatment at lower total treatment costs, mainly due to higher adherence rates with once-daily ICS dosing strategy (51). Consequently, relatively simple interventions administered during an office visit may help to modify misconceptions about asthma and medications, in order to achieve higher adherence rates and eventually better asthma control.

All the above considerations suggest that optimal adherence, although difficult, is an achievable target. The fact that an optimal level of adherence is a difficult target to achieve does not mean that we shouldn't try or that we should take the easy, costly, and highly inefficient way of stepping up therapy.

Inhaler administration technique

Another modifiable factor that is also associated with poor asthma control is the inhaler administration technique. Although inhaler administration technique is usually incorporated into assessment of adherence to controller therapy because true adherence to inhaled therapy involves both taking the right quantity of medication and doing it in the correct manner (17), we preferred to analyze it separately, because the reasons for an inadequate inhaler technique could be different from those for not giving inhalers to children as prescribed (52).

An appropriate technique for administering an inhaler is critical for achieving an optimal therapeutic effect, with evidence showing that an inadequate inhaler technique is associated with a decrease in lung deposition from 20% to 7%, a suboptimal therapeutic effect, and an increase in the side effects of inhaled medications (53–55). In order to reduce problems associated with the coordination and inhalation of medications in pediatric patients, it is highly recommended that inhalers be used in conjunction with valved holding chambers or spacers with an appropriate mouthpiece or a well-fitting face mask (56). It is important to mention that healthcare providers need to match patients to their preferred controller medication device based on the characteristics of the device and the child's ability to use it correctly. Depending

on the child's cognitive development, including his or her general cognitive ability and executive functions, several skills are considered critical or essential for effective delivery of inhaled medications to appropriate areas of the lung, which poses many different challenges and complex issues associated with this delivery in children when compared with adult patients. These skills comprise the following: quiet tidal breathing without crying or screaming, a slow, deep inhalation followed by an occasional holding of the breath, holding the breath during a phase of the breathing cycle (inhalation/exhalation) or before, during, or after canister actuation (when using a chamber with mouthpiece), and the closing of the mouth around the mouthpiece or a good face-mask fit in order to get an adequate seal. In addition to these procedures, there is a series of steps that must be taken in the proper sequence, such as shaking the inhaler before its administration and the correct attachment of the spacer device to the inhaler (52,57).

The multiple complex issues, skills, and steps required for an adequate inhaler technique in children can be a cause of confusion for pediatric clinicians, resulting in an inadequate inhaler technique assessment. In addition, physicians and trainees may have a poor understanding of how to use these devices (58), which will contribute to providers' not feeling that they have the ability to effectively assess inhaler technique. This could result in failure to identify inefficient inhaler technique as a contributing cause of poor asthma control, resulting in, or in conjunction with, the inability to detect nonadherence to controller therapy, inappropriate investigations, and escalation of treatment (57).

Like many other health measures, it is essential to have an accurate measurement of the inhaler administration technique, despite its difficulty. As a help in dealing, at least partially, with the problem of assessing the adequacy of the inhaler technique, several instruments (scales, checklists, or questionnaires) have been developed, grouping much of the above-mentioned skills and steps (57). The skills and steps contained in these instruments have been derived from previous scales, review of the literature, clinical experience, and recommendations given by biomedical research agencies. Although these instruments could be used and recommended as objective measurements of the adequacy of inhaler technique in the clinical and research contexts, unfortunately in only a minority of them is there a specific measurement or report of their measurement properties, mainly reliability, utility, and validity (57). Consequently, we encourage pediatric clinicians and researchers not only to educate themselves about how to properly use these

devices, but also to adopt these instruments in clinical practice or for research purposes and to perform additional evaluations of their measurement properties in order to ensure appropriate validity and reliability within the specific context in which the instrument will be used. Again, asthma educational interventions that incorporate behavioral components and reinforcements over time are potentially helpful in improving inhaler administration technique (59).

Cost-effectiveness issues

Although there is indeed evidence showing the clinical efficacy of biologic therapy for the treatment of uncontrolled pediatric asthma despite optimal pharmacological treatment (60), it is also true that there is evidence suggesting that adequate adherence to controller medication would have resulted in improved asthma control and eliminated the necessity to start a biologic therapy (61). In support of this observation, there are reports of considerable differences in the percentage of children for whom the use of omalizumab has been indicated between different clinics for difficult asthma, with a lower use of omalizumab in the clinics that employ a systematic approach to the evaluation of patients, including a rigorous assessment of the level of therapeutic adherence to controller medication (62). Additionally, a 2018 report from the Institute for Clinical and Economic Review (ICER) concluded that to be considered cost-effective, the prices of biologic therapies would have to be reduced by 62% to 80% of their current wholesale acquisition prices (63). This is in good agreement with a more recent study that concluded that the addition of omalizumab is not a cost-effective strategy compared with standard therapy for children with severe allergic asthma in China due to its high cost (64). Biologic therapy represents the end of the spectrum of the inappropriate escalation of controller therapy in patients with inadequate assessment and/or treatment of suboptimal adherence to controller therapy and/or poor inhaler technique. Therefore, the same problem occurs with other treatments more expensive than ICS, such as combined therapy using ICS and a long-acting β_2 agonist, tiotropium, etc. Nevertheless, biologics are used as a reference for comparison due to their high cost and the disproportionate increase in their use in recent years (62). At this point, it is worth mentioning that part of the effectiveness of biologics could be because of their total degree of therapeutic adherence due to their administration route (e.g. subcutaneous) that is effectively directly observed therapy (65). Taken together,

these facts suggest that in many cases we are overcoming our inability to have pediatric asthmatic patients take a class of medications that are simultaneously highly effective and inexpensive (e.g. ICS) by escalating their therapy to the use of biologics. Although this inappropriate resource use is always inadvisable and unacceptable, it is even more so in LMICs, given the serious challenges that typically need to be overcome in these countries, such as significantly higher disease burdens, numerous competing critical priorities, limited administrative capacity, and serious constraints in financing essential health services, especially in rural areas (66). Promoting the rational and cost-effective use of asthma controller therapy could help to optimize the limited health resources in many countries in which the inappropriate and unnecessary use of costly medications on the one hand and the inadequate provision of primary care services on the other perpetuate the inequality (67).

In a similar manner, although due to the high prevalence and the huge economic burden of pediatric asthma, especially difficult-to-treat asthma (8), it is highly probable that the use of EMDs is cost-effective, even in LMICs, it is unlikely that EMDs will be used in routine clinical practice in the near future in most countries. Because of the huge costs incurred when unnecessary requests for expensive diagnostic tests and escalation of treatment are the result of a failure to detect nonadherence to controller therapy due to the use of methods that overestimate the true level of adherence (18), it is highly probable that the use and implementation of EMDs is cost-effective and cost-saving. This is because it is highly probable that cost savings derived from distinguishing poor adherence from poor treatment response to ICS outweigh the cost of objective adherence measurement using EMDs (24). In addition, it is also probable that wide-scale use of EMDs in the future would lead to reduced costs, which would further increase its cost-effectiveness (39). Nevertheless, this must be proven through formal cost-effectiveness analyses. Finally, as suggested above, empathy and a true and strong physician-parent/patient partnership have a more powerful influence on adherence than almost any other factor (68), and they are probably the most cost-effective methods not only for detecting poor adherence to controller therapy but also for dealing with and improving it. This concept is supported by studies showing suboptimal levels of adherence in asthmatic children despite knowing they were being monitored with EMDs (32). Consequently it is highly probable that

the potential cost savings derived from building a true partnership with patients (and their parents) and the consequent improvement in adherence and clinical outcomes outweigh the apparent cost savings resulting from shortening office visits in order to see

more patients in less time (35), which is a common practice in LMICs.

Based on all the above-mentioned considerations, we propose a management algorithm for children with persistent asthma (Figure 1).

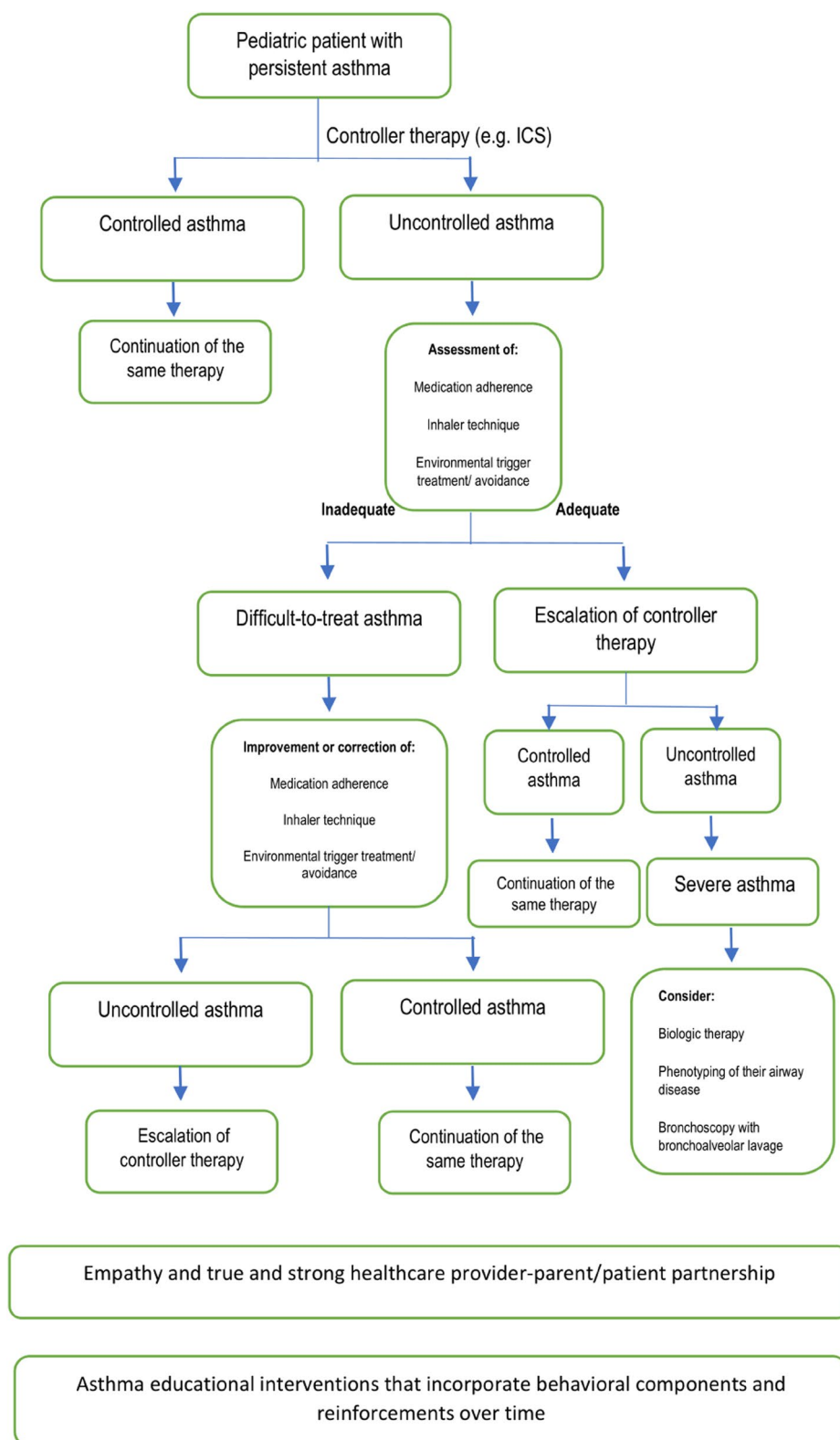


Figure 1. Proposed management algorithm for children with persistent asthma.

Discussion and conclusion

Despite relatively recent advances in our understanding of the pathophysiology of asthma and the availability of highly effective controller medications such as ICS, currently many pediatric patients fail to control their asthma. Although some of these difficult-to-treat asthmatic children have severe therapy-resistant asthma, most of them experience poor asthma control due to various modifiable factors, among which poor adherence to inhaled controller therapy and inadequate inhaler technique are the most common. Although improving adherence to ICSs is an important target in asthma care because non-adherence to treatment compromises its effectiveness and drives up healthcare costs, methods of assessing adherence must be as accurate and objective as possible. Although EMDs have been considered to be essential tools in identifying children with severe therapy-resistant asthma, their high cost and low availability have currently limited their use in many countries, especially LMICs. For these reasons, we encourage the weighing of inhaler canisters and self-reported validated questionnaires as alternative and valid options for assessing adherence to inhaled controller therapy. Furthermore, we encourage the use of validated instruments as an objective measurement of the adequacy of inhaler technique. Although recognizing poor adherence does not automatically lead to improved adherence, it is usually an essential first step in effectively targeting adherence behavior, especially if the reasons for low or erratic compliance are explored by means of non-judgmental healthcare provider-patient communication. These recommendations could assist in overcoming our inability to have pediatric asthmatic patients use ICS and in avoiding escalating their controller therapy toward more expensive medications, eventually reaching the use of biologics. Promoting the rational and cost-effective use of asthma controller therapy could help to optimize the limited health resources in many LMICs.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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