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REVIEW ARTICLE OPEN

How to match the optimal currently available inhaler device to an individual child with asthma or recurrent wheeze

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Inhaled medications are the cornerstone of treatment in early childhood wheezing and paediatric asthma. A match between patient and device and a correct inhalation technique are crucial for good asthma control. The aim of this paper is to propose an inhaler strategy that will facilitate an inhaler choice most likely to benefit different groups of children. The main focus will be on pressurised metered dose inhalers and dry powder inhalers. In this paper we will discuss (1) practical difficulties with the devices and with inhaled therapy and (2) the optimal location for deposition of medicines in the lungs, and (3) we will propose a practical and easy way to make the best match between the inhaler device and the individual patient. We hope that this paper will contribute to an increased likelihood of treatment success and improved adherence to therapy.

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INTRODUCTION

Inhaled medications are the cornerstone of treatment in early-childhood wheezing and paediatric asthma. They should be targeted to areas in the lungs where they will be most effective. Treating paediatric asthma (children aged 5 years or older) with inhaled corticosteroids (ICSs) and bronchodilators has resulted in improvements in asthma control.[1] In early-childhood wheezing (0–4 years), treatment outcomes are less positive probably because of diverse clinical phenotypes. In this young age it is difficult to achieve and maintain an optimal inhalation technique.[2,3]

The most important advantage of inhaled delivery of medicines is that they are delivered directly into the airways and lungs, resulting in higher local concentrations, lower systemic exposure and fewer systemic side effects compared with the oral or intravenous route. However, inhalation of medicines can be complicated and difficult for some children. Drug deposition in the lungs depends on the type of inhaler device, the characteristics of the inhaled medicine, and on patient-related characteristics.[4]

There are many reports of treatment failure due to poor inhalation technique.[5] The number of inhalation devices is immense. Physicians and pharmacists who prescribe and supply them may lack knowledge on the best choice of device for each individual or may be unaware of the specific inhalation technique that best matches the patient's needs.

Several studies have demonstrated that large numbers of patients do not use their inhalers correctly, thereby gaining little or no therapeutic benefit from the prescribed treatment.[6–8] Focussing on which inhalers are the easiest to use correctly by children of varying ages is at least as important as the *in vitro* output characteristics of any inhaler. Because of patient heterogeneity, no single inhaler will satisfy the needs of all. This is particularly true in children where different age groups possess different psychomotor skills. Cost is another important consideration, but will vary from country to country and is beyond the scope of this review.

The aim of this paper is to propose an inhaler strategy that will facilitate an inhaler choice most likely to benefit different groups of children. The main focus will be on pressurised metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs), highlighting practical difficulties with the devices and with inhaled therapy. In addition, we will discuss the optimal location for depositing the medicines in the lungs. Finally, we will propose a practical and easy way to make the best match between the inhaler device and the individual patient. The hope is that this will improve consistency of inhaler prescribing in primary and secondary care, in children with early-childhood wheeze and asthma (Box 1).

DIFFICULTIES WITH INHALED THERAPY

A device that is easy to use and also allows optimal lung deposition seems crucial for disease control. This is particularly important for ICSs and short-acting β_2-agonists.

The optimal inhalation technique differs between devices. Many children experience problems using their inhaler correctly, resulting in poor asthma control.[5] Meta-analyses (including studies in children from 7 months and older) indicate that if the correct inhaler technique is taught, different devices produce similar clinical outcomes.[9,10] However, patients and parents were well trained in device usage and some were excluded if they were unable to inhale correctly.

Poor inhaler technique was found in 70% of 3,955 asthma patients who used a pMDI and was associated with decreased asthma stability.[6] Other studies have reported poor inhaler technique in 32–96% of patients.[7,11] Inhalation technique often remains poor after several teaching sessions.[10] Comprehensive training and repeated checks are needed to ensure a reliable inhalation technique.[12] Many physicians have poor knowledge and training in the correct use of inhaler devices,[13] resulting in

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Box 1 Manuscript selection

This review contains many different subjects that are often substantiated by limited evidence in the literature, such as device characteristics, optimal inhalation technique for a specific device, age specificity of devices and so on. Many devices lack documentation of their characteristics. Other factors that may influence an optimal outcome of inhaled therapy are the limited knowledge of physicians about the different devices and adherence to treatment. For this reason no systematic review was performed.

We aimed to write a practical guide for optimal inhalation for the individual child. Advice is based on the scientific and clinical experience of the authors, including a review of relevant references from the recent European Respiratory Society task force on inhalation devices.[4]

inconsistency in the choice of inhaler device and lack of explanation and training.

Education and perception

Before starting inhaled therapy, an explanation about the aims of treatment must be given. The key question to ask when regular, preventative therapy fails is whether the child is actually taking the medication. Parents are naturally concerned about the possible side effects of ICSs, such as growth retardation and dependence on medicines.[14,15] A recent long-term follow-up study in children with asthma who were treated for at least 4 years with budesonide (BUD) or nedocromil indicated that children who used ICSs were 1 cm shorter with respect to their final height compared with the group that used nedocromil (a non-steroid anti-asthma drug).[16] Possible barriers need discussion; a dialogue between careprovider and family should result in a shared perception about the disease and its treatment goals leading to a good starting point for eventual successful management and control.[17–19]

Requirements for inhalation

The requirements for inhalation are different for very young children. The deposition in the lower airways during crying is markedly reduced.[20,21] The facemask seal is critical for efficient aerosol delivery to infants and young children.[22,23] There are also differences in anatomy and physiology of the upper airways: the pharynx and supraglottic area are less rigid; the epiglottis is narrow and floppy and closer to the palate; and the larynx is higher and close to the base of the tongue.[3] Delivery through the nose has been shown to be less effective than through the mouth, probably because of higher resistance, the high flow rate and increased turbulence in the nostrils and the nasopharynx.[24,25] High inspiratory flows cause impaction of drug particles in the upper airways, especially the larger particles (3–5 μg).[26] Smaller particles, inhaled with lower inspiratory flows, have a greater chance to bypass the upper airways and deposit in the lower airways. Young children are not able to hold their breath and are more likely to exhale much of their medication. Amirav *et al.* reviewed the differences in lung deposition of aerosol therapeutics with large and small particles and concluded that small-particle aerosols provide better deposition than larger ones in young children.[3]

Children 7 years and older usually have a sufficient inspiratory flow rate to inhale through all of the different types of inhalers, such as pMDI–spacer combinations, breath-actuated inhalers (BAI) and DPIs.

Current prescribing shows a range of devices being used, some of which may have advantages in certain patients over a pMDI plus spacer, and we have therefore set out to explain when they can and cannot be used.

PRACTICAL DIFFICULTIES IN THE USE OF INHALERS

Pressurised metered-dose inhalers

These are widely used in the treatment of childhood asthma and in young children with recurrent wheezing. An aerosol dose is generated by the patient pressing down the canister into the actuator seating. Canisters of suspension aerosols should be shaken. A good press and breathe (hand–breath) coordination is needed to inhale the medication into the peripheral airways. With the introduction of HydroFluoroAlkane propellants, some aerosols kept their initial characteristics (large particle size, high velocity), such as fluticasone propionate (FP) and beclomethasone dipropionate (BDP; Clenil, GlaxoSmithKline, London, UK), but some aerosols have changed characteristics; for example, extra-fine HydroFluoroAlkane BDP (Qvar, Teva Pharmaceuticals, Tel Aviv, Israel) changed to a smaller median mass aerodynamic diameter ('median particle size'; 1.1 μm).

The use of a pMDI looks simple: 'press and breathe'. However, it is complex because it requires hand–breath coordination and the need to breath-hold afterwards. Poor hand–breath coordination results in reduced lung deposition.[26] Almost all children and adults with asthma have problems in coordinating the pMDI actuation together with their inhalation of the released aerosol.[27–29] One way to solve this poor coordination is the use of a valved holding chamber or spacer.[30] Another possibility in children 7 years or older and in adults is a breath-actuated device.[31]

Breath-holding after inhalation is essential for an optimal deposition of the inhaled medication in the smaller airways.[32] A breath-hold pause of 5 s is suggested in children up to 10 years of age. This recommendation is based on a study in trained 5–17-year-old children who inhaled extra-fine HydroFluoroAlkane BDP via an AeroChamber-Plus (Trudell, London, ON, Canada) with a mouth piece.[30] Lung (filter) deposition was highest in the group that breath-held (56.6% in 5–7-year-olds, 56.6% in 8–10-year-olds, and 58.4% in 11–17-year-olds) compared with the group that took five tidal breaths (35.4% in 5–7-year-olds, 47.5% in 8–10-year-olds and 54.9% in 11–17-year-olds).

pMDI–spacer combination

pMDI–spacer combinations can be used by almost everyone. They overcome hand–breath coordination difficulties and decrease oropharyngeal deposition, thereby increasing deposition into the lower airways. Because the larger aerosol particles deposit in the spacer, local unwanted side effects in the mouth and throat, such as thrush and hoarseness, are much reduced.

The volume of the spacer is important, especially for young children with low tidal volumes. Higher aerosol concentration in the smaller volume chambers increases drug delivery to where it is needed.[33] Multiple breaths may also increase drug delivery into the airways. Schultz *et al.*[34] recorded the breathing patterns in 2–7-year-old children inhaling placebo using four different spacers. Two tidal breaths were adequate to inhale the aerosol using small-volume spacers (Aerochamber Plus, Funhaler, ITL design & Manufacturing, Eveleigh NSW, Australia) and three tidal breaths were adequate using the larger spacer (Volumatic, GlaxoSmithKline).

Other factors also influence the variation in the delivered dose. The electrostatic charge in a spacer reduces delivery into the lung. In a randomised crossover study Janssens *et al.*[35] investigated children with stable asthma aged 1–4 years and 5–8 years. They assessed the dose variability delivered to the mouth through a metal Nebuchamber (AstraZeneca, Luton, UK) (no electric charge)

and through two plastic spacers: the Babyhaler (Glaxo Wellcome, Greenford, UK) in 1–4-year-olds and the Volumatic in 5–8-year-olds. They found substantial within-subject dose variability in aerosol delivery. The variability was lower for the metal spacer (currently rarely used) than for the plastic spacer in the 5–8-year age group. The dose delivered to the mouth through the metal spacer was twice that delivered through the plastic spacers.

The dose delivered through a spacer also varies with a child's age and with the child's breathing pattern. Lung deposition was determined in two groups of asthmatic children. All inhaled five puffs of radio-labelled salbutamol pMDI through a plastic spacer: the younger group (up to 48 months) used a Babyhaler with a facemask and the older group (⩾48 months) used a Volumatic. The younger children used five tidal breaths between actuations. The older children inhaled with five tidal breaths or one single slow breath with maximal inhalation and held their breath for 10 s. Lung deposition varied from 16.4% in the younger children to 28.2 or 41.8% in the older group inhaling with different breathing patterns.[36] Table 1 shows the wide differences in lung deposition in children inhaling with a pMDI and spacer combination and with different breathing patterns.

The practical conclusion that can be drawn from these data is that young children up to 7 years most benefit from inhalation with small-volume spacers.[33,37] Most children aged 4 years or older (and sometimes even younger) can use a spacer with a mouthpiece, and the younger children should use a spacer with a mask. Children aged 4 years or older are able to hold their breath for 5–7 s, which improves the lung deposition of the drug.

Breath-actuated inhalers

Breath-actuated metered dose inhalers may overcome hand–breath coordination problems. They release a dose of aerosol triggered by a relatively low inspiratory flow rate (Autohaler 30 l/min (3M, St Paul, MN, USA), Easibreath (PA, London, UK) or Redihaler 20 l/min (Teva Pharmaceuticals, Waterford, Ireland)). They contain extra-fine HydroFluoroAlkane BDP or salbutamol. Because of the short and limited inspiratory flow of young children they are advised to be used in children aged 7 years or older. A deposition study in children aged 5–14 years showed an age-dependent lung deposition from 36.9% up to 54.1% in the older children.[38,39]

Dry powder inhalers

DPIs, such as the Turbuhaler (Astra Zeneca, Lund, Sweden) and the Diskus (GlaxoSmithKline), require a rapid and forceful inhalation. Medication is delivered to the lungs after a deep inhalation through the DPI. Most DPIs contain micronised drug blended with larger lactose particles. These particles are too large to be inhaled, and hence release of the drug particles from carrier particles is needed. The energy for dispersion is derived from the inhaled airstream. The more forceful the inspiratory flow through the DPI, the higher the fraction of released drug particles, the higher the total lung dose and the greater the fine particle fraction.[40] The advantage of DPIs in children with sufficient inspiratory flow is that they overcome hand–breath coordination problems. Disadvantages are that the delivered dose is inspiratory flow and acceleration dependent. Another disadvantage in younger children (e.g., 4–6 years old) is that inhalation may be effective when the child is well but may be insufficient during a period of wheezing.[41]

The variability of the delivered dose from DPIs is greater than that from pMDIs.[40] The median mass aerodynamic diameter of the Turbuhaler with a low flow (30 l/min) was 6.23 μm, whereas it decreased to ~2.28 μm with an inspiratory flow of 60 l/min.[40] When the Diskus and Turbuhaler were compared for the delivery of FP and BUD, the results showed that the Diskus delivered 87–93% of the label claim, whereas the Turbuhaler delivered 40–58%.[42] Increasing the inspiratory flow through the Turbuhaler from 30 l/min to 60 l/min and to 90 l/min resulted in an increase in BUD delivery from 37.5 to 64.4 to 107.4% of the label claim dose, and the fine particle mass more than doubled.[41] In the only *in vivo* study, Agertoft and Pedersen compared the lung deposition of BUD inhaled from the Turbuhaler and that of FP inhaled from

Table 1. Mean lung deposition in children with a pMDI spacer combination

Author/Journal	*Age*	*Device*	*Breathing pattern*	*Drug*	*Mean lung deposition*
Agertoft and Pedersen[37]	10–25 mo	Nebuhaler (750 ml)	30 s tidal breathing	Budesonide	26.7% (17–44)
Arch Dis Child, 1994		Aerochamber	30 s tidal breathing		19.7% (9–33)
		Babyspacer	30 s tidal breathing		27.7% (19–38)
Tal *et al.*[55]	0.25–5 y	pMDI -Aerochamber	30 s tidal breathing	Salbutamol	1.97% (1.4)
J Pediatrics, 1996					
Wildhaber *et al.*[56]	2–4 y	pMDI- Aerochamber	5 Tidal breaths	Salbutamol	5.4% (2.1)
J Pediatrics, 1999	5–9 y		in the 5–9-y group		9.6% (3.9)
Wildhaber *et al.*[36]	< 48 mo	Babyhaler	Tidal breathing	Sabutamol	16.4% (5.5)
J Pediatrics, 2000	⩾48 mo	Volumatic	Tidal breathing		28.2% (6.7)
		Volumatic	Single breath		41.8% (3.8)
Roller *et al.*[30]	5–7 y	Aerochamber	Tidal breathing	Extra-fine HFA beclomethasone	35.4% (8.3)
Eur Respir J, 2007	8–10 y	Aerochamber	Breath-hold	Extra-fine HFA beclomethasone	47.5% (13.0)
	11–7 y				54.9% (11.2)
	5–7 y				58.1% (6.6)
	8–10 y				56.6% (5.2)
	11–7 y				58.4% (9.2)
Schulz *et al.*[34]	2–7 y	Aerochamber plus	2 Tidal breaths	Salbutamol	40% (95% CI: 34–46%)
Pediatrics, 2010			9 Tidal breaths		41% (95% CI: 36–47%)
			Funhaler		39% (95% CI: 34–43%)
			2 Tidal breaths		38% (95% CI: 35–42%)
			9 Tidal breaths		37% (95% CI: 33–41%)
			Volumatic		43% (95% CI: 40–46%)
			2 Tidal breaths		
			9 Tidal breaths		

Mean lung deposition (Agertoft), expressed as a percentage of the metered dose ± range, or (Schulz) as 95% confidence interval (CI), or (Tal, Wildhaber, Roller) expressed as s.d.
Abbreviations: HFA, hydrofluoroalkane-134a; pMDI, pressurised metered-dose inhaler.

Diskus.[43] The mean lung deposition in children aged 8–14 years after Turbuhaler and Diskus inhalation was 30.8 and 8%, respectively, when inhalation of BUD and FP took place on separate days and 29.5 and 7.6%, respectively, when inhaled on the same day. These *in vivo* data indicate a fourfold higher deposition from Turbuhaler than from Diskus.[43] In another study in which the breathing pattern of 4–8-year-old children was simulated,[44] the total emitted dose of FP Diskus was compared with that of BUD Turbuhaler. An overall 87–89% of the label claim was emitted from the Diskus compared with 56–62% from the Turbuhaler. However, the fine particle fraction was slightly lower from the Discus compared with the Turbuhaler (15–18% vs. 21–23%). For both devices, there was an inverse relationship between inspiratory flow rate and particle size

The Novolizer (Sofotec GmbH & Co. KG, Frankfurt, Germany) is a more recently developed breath-activated multidose refillable DPI with dose counter. It has the advantage of a feedback mechanism that guides the patient through the correct inhalation manoeuvre.[45] A study in 4–11-year-old children showed that they were capable of generating twice the minimal PIF (35–50 l/min) to overcome the trigger threshold of the Novolizer.[46] The novolizer may contain BUD, salbutamol or formoterol. The particle size dependency of the flow rate is less apparent in the Novolizer as in other DPIs.[45]

However, clinical head-to-head studies in different age groups should be performed to investigate whether these differences have any clinical relevance.

Table 2 shows an age indication of the different types of inhalers.

WHERE SHOULD INHALED CORTICOSTEROIDS AND β_2-AGONISTS BE DELIVERED?

The most important inhaled medicines for the treatment of asthma and early-childhood wheezing are β_2-adrenergic bronchodilators and ICSs. The inflammatory process involves the entire airway and, as corticosteroid receptor density increases in the peripheral airways,[47] ICS delivery to small airways is important. As β_2 receptors are found equally in the large and smaller airways, targeting wide areas of the airways may be important for bronchodilators as well.[48,49]

Small-particle ICSs, such as ultra-fine HydroFluoroAlkane BDP aerosol and ciclesonide, may offer a potential benefit in young children with smaller airways.[50] These characteristics may be particularly relevant in young children in whom more airways are classified as small (<2 mm in diameter) and whose airway resistance is high.[51]

Recommended doses according to the GINA guidelines are shown in Table 3.

MAKING THE OPTIMAL MATCH BETWEEN INHALATION DEVICE AND THE INDIVIDUAL PATIENT

Before prescribing an inhaler device the following questions may be helpful to choose the correct device for the individual patient.

Table 2. Age indication of the different types of inhalers

	0–3 y	*4–6 y*	*7 y and older*
pMDI	+ Spacer (small) with mask 10 times tidal breathing	+ Spacer (small) with mouth piece 2 deep breaths 5–7 s breath-holding	+ Spacer with mouth piece 1 deep breath 7 s breath-holding
DPI	–	–	Quick and forcefully deep inhalation 5–7 s breath-holding
BAI	–	–	Normal deep inhalation 5–7 s breath-holding

Abbreviations: BAI, breath-actuated inhaler; DPI, dry powder inhaler; pMDI, pressurised metered-dose inhaler.

Table 3. Dose indication of different inhaled corticosteroids

Equipotent doses of ICS for adults and children older than 5 years					*Low daily doses of ICS in children ⩽ 5 years*	
Drug	*Low dose (μg)*	*Medium daily dose (μg)*	*High daily dose (μg)*	*Products available in different countries*	*Drug*	*Low daily dose (μg)*
Beclomethasone dipropionate—CFC	200–500	>500–1,000	>1,000–2,000	Beclomethasone Clenil Becotide	Beclomethasone dipropionate	100
Extra-fine Beclomethasone dipropionate—HFA	100–250	>250–500	>500–1,000	Qvar Aerobec	Budesonide MDI+spacer Budesonide nebulised	200 500
Budesonide[a]	200–400	>400–800	>800–1,600	Budesonide Pulmicort	Ciclesonide[a]	Not studied in this age group
Ciclesonide[a]	80–160	>160–320	>320–1,280	Alvesco	Fluticasone propionate	100
Flunisolide	500–1,000	>1,000–2,000	>2,000	Aerobid	Mometasone furoate	Not studied in this age group
Fluticasone propionate	100–250	>250–500	>500–1,000	Fluticasone Flixotide	Triamcinolone acetonide	Not studied in this age group
Mometasone furoate[a]	200	>400	>800	Asmanex		
Triamcinolone acetonide	400–1,000	>1,000–2,000	>2,000	Triamcinolone		

Comparisons based on efficacy data. Doses according to GINA guidelines.[1]
Abbreviation: ICS, inhaled corticosteroid.
[a]Approved for once daily dosing in mild patients.

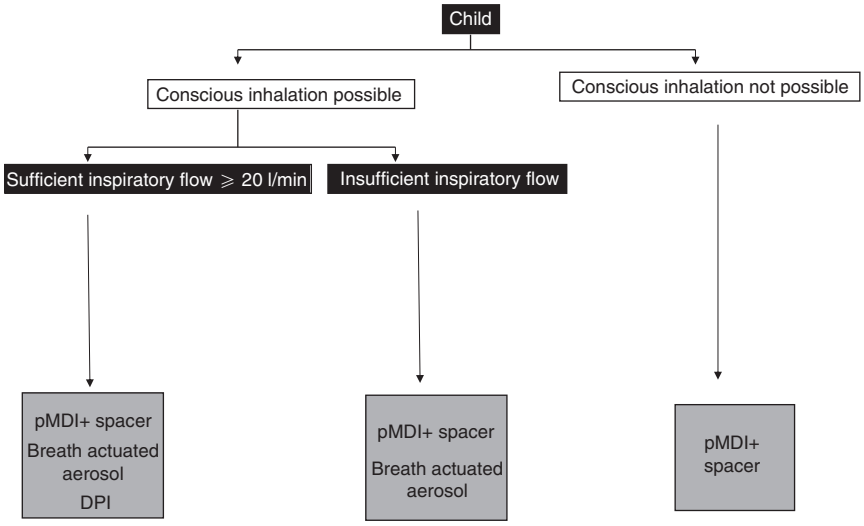

Figure 1. Algorithm for the optimal choice for an inhaler device. pMDI, pressurised metered-dose inhaler; DPI, dry powder inhaler.

Who?

What is the age of the child? Can he/she consciously inhale? Young infants and disabled children are not aware how to inhale. Young children have a low inspiratory flow and are not able to hold their breath.

Where?

In children with asthma and in those with early wheezing the small airways should be targeted. Small-particle ICSs may have an advantage because of higher deposition in the small airways.[3] The clinical relevance in children for small-particle drugs is weak and mainly based on the findings from a double-blind randomised controlled trial and from one real-life study. In a double-blind randomised controlled dose reduction study in school-aged children, extra-fine HydroFluoroAlkane BDP pMDI plus spacer proved to be equally effective compared with FP pMDI plus spacer.[52] However, in a real-life comparative effectiveness study, increasing the extra-fine HydroFluoroAlkane BPP dose appeared to provide improved outcomes (significantly better asthma control and significantly fewer exacerbations) compared with stepping up ICS as FP or adding a separate long-acting beta-agonist (significantly better asthma control); similar outcomes were seen when compared with a fixed-dose combination of ICS/long-acting β_2-agonist.[53]

How?

Age can act as a relative proxy for insufficient inspiratory flow. Under 7 years of age there is insufficient inspiratory flow to inhale a DPI or a BAI; it is also not possible to teach these young children to hold their breath.[54] The only options here are a pMDI–spacer combination, with tidal breathing (5–10 times) after actuation. Medicines delivered through nebulisers should not be used as first-line prescriptions in primary care because higher dosages are licensed with a greater possibility of adverse effects and expense. Especially short-acting β_2-agonists in very young children should be nebulised with oxygen rather than air as the flow gas because of the danger of arterial oxygen desaturation.

A DPI or a BAI can be used from 7 years of age. The problem with a breath-actuated device in children from 4 to 6 years of age is that their inspiration time is too short to complete an effective inhalation.

For children aged 3 years or lower, a pMDI–spacer combination with a face mask can be used. In children aged 4 years or older, a pMDI–spacer combination with a mouth piece is preferred. Above 6 years of age many different inhalers may be effective.

The optimal choice for an inhaler device can be summarised in the following two questions and in the use of one algorithm (Figure 1) to make the correct choice for the individual patient.

1. Is the patient conscious of his/her inhaling?
   Young children (6 years or younger) or children who are mentally not able to follow instructions about a correct inhalation technique should use a pMDI plus spacer and not a pMDI without a spacer, DPI or breath-actuated aerosol.
2. Is his/her inspiratory flow sufficient?
   Young children with an insufficient inspiratory flow (6 years or younger) or children with insufficient muscular power to inhale forcefully should not use DPIs or breath-actuated aerosols.

CONCLUSION

A wrong inhaler technique or inhaler device is one of the most prevalent causes of poor asthma control. An optimal choice for the individual patient, device training and repeated checks of patients' device use and technique are essential for good asthma control.

CONTRIBUTIONS

WMvA wrote the first draft; all authors helped to improve the manuscript and contributed equally to the manuscript.

COMPETING INTERESTS

WMvA is a member of the advisory boards of Mundipharma, Astra Zeneca, AbbVie and Teva. LGM has no conflict of interest. MG has no conflict of interest. WL has no conflict of interest. S. Pedersen has received consultancy fees from Glaxo Smith Kline and Boehringer Ingelheim, and fees for lectures for Glaxo Smth Kline and Boehringer Ingelheim. PND has received reimbursements for attending symposia, fees for speaking, organising educational events, funds for research or fees for consulting from AstraZeneca, Boehringer-Ingelheim, Chiesi, Merck Sharp & Dohme, Mundipharma, Novartis, Takeda, Almirall and Teva. He is a member of the Aerosol Drug Management Improvement Team (ADMIT). DP has board membership at Almirall, Astra Zeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Mundipharma, Medapharma, Novartis, Napp, Nycomed, Pfizer, Sandoz and Teva. *Consultancy*: Almirall, Amgen, Astra Zeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Mundipharma, Medapharma, Novartis, Napp, Nycomed, Pfizer, Sandoz and Teva. *Grants/Grants Pending*: UK National Health Service, Aerocrine, Astra Zeneca, Boehringer

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REFERENCES

1 GINA report. Global Strategy for the Diagnosis and Management of Asthma in children. Updated 2009 and 2012 www.ginasthma.org.
2 Kaditis AG, Winnie G, Syrogiannopoulos GA. Anti-inflammatory pharmacotherapy for wheezing in preschool children. *Pediatr Pulmonol* 2007; **42**: 407–420.
3 Amirav I, Newhouse MT, Minocchieri S, Castro-Rodriguez JA, Schüepp KG. Factors that affect the efficacy of inhaled corticosteroids for infants and young children. *J Allergy Clin Immunol* 2010; **125**: 1206–1211.
4 Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P *et al.* What the pulmonary specialist should know about new inhalation therapies. *Eur Respir J* 2011; **37**: 1308–1331.
5 Ammari WG, Chrystin H. Optimizing the inhalation flow and technique through metered dose inhalers of asthmatic adults and children attending a community pharmacy. *J Asthma* 2013; **50**: 505–513.
6 Hagmolen of ten Have W, Van de Berg NJ, Bindels PJ, van Aalderen WM, van der Palen J. Assessment of inhalation technique in children in general practice: increased risk of incorrect performance with new device. *J Asthma* 2008; **45**: 67–71.
7 Pedersen S, Dubus JC, Crompton GK, ADMIT Working Group. The ADMIT series issues in inhalation therapy. 5) Inhaler selection in children with asthma. *Prim Care Respir J* 2010; **19**: 209–216.
8 Harnett CM, Hunt EB, Bowen BR, O'Connell OJ, Edgeworth DM, Mitchell P *et al.* A study to assess inhaler technique and its potential impact on asthma control in patients attending an asthma clinic. *J Asthma* 2014; **51**: 440–445.
9 Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL *et al.* Device selection and outcomes of aerosol therapy: Evidence based guidelines: American college of chest physicians/American college of Asthma, Allergy, and Immunology. *Chest* 2005; **127**: 335–371.
10 Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L *et al.* Comparison of effectiveness of inhaler devices in asthma and chronic obstructive airway disease: a systematic review of the literature. *Health Technol Assess* 2001; **5**: 1–149.
11 Inhaler Error Steering Committee, Price D, Bosnic-Anticevich S, Briggs A, Chrystyn H, Rand C *et al.* Inhaler competence in asthma: common errors, barriers to use and recommended solutions. *Respir Med* 2013; **107**: 37–46.
12 Kamps AW, Brand PL, Roorda RJ. Determinants of correct inhalation technique in children attending a hospital based asthma clinic. *Acta Paediatr* 2002; **91**: 159–163.
13 Hanania NA, Wittman R, Kesten S, Chapman KR. Medical personnel's knowledge of and ability to use inhaling devices. *Chest* 1994; **105**: 111–116.
14 Rau JL. Determinants of patient adherence to an aerosol regimen. *Respir Care.* 2005; **50**: 1346–1356.
15 Horne R. Compliance, adherence, and concordance: implications for asthma treatment. *Chest* 2006; **130**(1 Suppl): 65S–72S.
16 Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, CAMP Research Group *et al.* Effect of inhaled glucocorticoids on adult height. *N Engl J Med* 2012; **367**: 904–912.
17 Bokhour BG, Cohn ES, Cortés DE, Yinusa-Nyahkoon LS, Hook JM, Smith LA *et al.* Patterns of concordance and non-concordance with clinician recommendations and parents' explanatory models in children with asthma. *Patient Educ Couns* 2008; **70**: 376–385.
18 Weinstein AG. The potential of asthma adherence management to enhance asthma guidelines. *Ann Allergy Asthma Immunol* 2011; **106**: 283–291.
19 Mauksch LB, Dugdale DC, Dodson S, Epstein R. Relationship, communication, and efficiency in the medical encounter: creating a clinical model from a literature review. *Arch Intern Med* 2008; **168**: 1387–1395.
20 Murakami G, Igarashi T, Adachi Y, Matsuno M, Adachi Y, Sawai M *et al.* Measurement of bronchial hyperreactivity in infants and preschool children using a new method. *Ann Allergy* 1990; **64**: 383–387.
21 Iles R, Lister P, Edmunds AT. Crying significantly reduces absorption of aerosolised drugs in infants. *Arch Dis Child* 1999; **81**: 163–165.
22 Amirav I, Newhouse MT. Aerosol therapy with valved holding chambers in young children: importance of the face mask seal. *Pediatrics* 2001; **108**: 389–394.
23 Amirav I, Newhouse MT. Review of optimal characteristics of face-masks for valve-holding chambers (VHC). *Pediatr Pulmonol* 2008; **43**: 268–274.
24 Chua HL, Collis GG, Newbury AM, Chan K, Bower GD, Sly PD *et al.* The influence of age on aerosol deposition in children with cystic fibrosis. *Eur Respir J* 1994; **7**: 2185–2191.
25 Cockroft DW, MacCormack DW, Tarlo SM, Hargreave FE, Pengelly LD. Nasal airway inspiratory resistance. *Am Rev Respir Dis* 1979; **119**: 921–926.
26 Howarth PH. Why particle size should affect clinical response to inhaled therapy. *J Aerosol Med* 2001; **14**(suppl): S27–S34.
27 Pedersen S, Frost L, Anfred T. Errors in inhalation technique and efficiency in inhaler use in asthmatic children. *Allergy* 1986; **41**: 118–124.
28 Plaza V, Sanchis J. Medical personnel and patient skill in the use of metered dose inhalers: a multicentric study. CESEA Group.. *Respiration* 1998; **65**: 195–198.
29 Pedersen S. Inhaler use in children with asthma. *Dan Med Bull* 1987; **34**: 234–249.
30 Roller CM, Zhang G, Troedson RG, Leach CL, Le Souëf PN. Spacer inhalation technique and deposition of extrafine aerosol in asthmatic children. *Eur Respir J* 2007; **29**: 299–366.
31 Newman SP, Weisz AW, Talaee N, Clarke SW. Improvement of drug delivery with a breath actuated pressurised aerosol for patients with poor inhaler technique. *Thorax* 1991; **46**: 712–716.
32 Leach CL, Colice GL. A pilot study to assess lung deposition of HFA-beclomethasone and CFC-beclomethasone from a pressurized metered dose inhaler with and without add-on spacers and using varying breathold times. *J Aerosol Med Pulm Drug Deliv* 2010; **23**: 355–361.
33 Everard ML, Clark AR, Milner AD. Drug delivery from holding chambers with attached face mask. *Arch Dis Child* 1992; **67**: 580–585.
34 Schultz A, Le Souëf TJ, Venter A, Zhang G, Devadason SG, Le Souëf PN. Aerosol inhalation from spacers and valved holding chambers requires few tidal breaths for children. *Pediatrics* 2010; **126**: e1493–e1498.
35 Janssens HM, Devadason SG, Hop WJC, Lesoueff PN, De Jongste JC, Tiddens HA. Variability in aerosol delivery via spacer devices in young asthmatic children in daily life. *Eur Respir J* 1999; **13**: 787–791.
36 Wildhaber JH, Janssen HM, Pierart F, Dore ND, Devadason SG, LeSouëf PN. High-percentage lung delivery in children from detergent-treated spacers. *Pediatr Pulmonol* 2000; **29**: 389–393.
37 Agertoft L, Pedersen S. Influence of spacer device on drug delivery to young children with asthma. *Arch Dis Child* 1994; **71**: 217–220.
38 Devadason SG, Huang T, Walker S, Trodson R, le Souëf PN. Distribution of technetium-99m-labelled QVAR TM delivered using an autohaler TM device in children. *Eur Respir J* 2003; **21**: 1007–1011.
39 Farmer IS, Middle M, Savic J, Perrin VL, Herdman MJ. Therapeutic equivalence of inhaled beclomethasone dipropionate with CFC and non-CFC (HFA134a) propellants both delivered via the EasibreatheTM inhaler for the treatment of paediatric asthma. *Respir Med* 2000; **94**: 57–63.
40 Ross DL, Schulz RK. Effect of inhalation flow rate on the dosing characteristics of dry powder inhaler (DPI) and metered dose inhaler products (pMDI). *J Aerosol Med* 1996; **9**: 215–226.
41 Pedersen S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. *Arch Dis Child* 1990; **65**: 308–310.
42 Hill LS, Slater AL. A comparison of the performance of two modern multidose dry powder asthma inhalers. *Respir Med* 1998; **92**: 105–110.
43 Agertoft L, Pedersen S. Lung deposition and systemic availability of budesonide Turbuhaler and fluticasone Diskus in children. *Am J Respir Crit Care Med* 2003; **168**: 779–782.
44 Bisgaard H, Klug B, Sumby BS, Burnell PK. Fine particle mass from the Diskus inhaler and Turbuhaler inhaler in children with asthma. *Eur Respir J* 1998; **11**: 1111–1115.
45 Fyrnys B, Stang N, Wolf-Heuss E. Stability and performance characteristics of a budesonide powder for inhalation with a novel dry powder inhaler device. *Curr Opin Pulm Med* 2001; **7**: S7–S11.
46 Vogelberg C, Kremer HJ, Ellers-Lenz B, Engel M, Maus J, Conrad F *et al.* Clinical evaluation of the peak inspiratory flow generated by asthmatic children through the Novolizer. *Respir Med* 2004; **98**: 924–931.

47 Adcock IM, Gilbey T, Gelder CM, Chung KF, Barnes PJ. Glucocorticosteroid receptor localization in normal and asthmatic lung. *Am J Respir Crit Care Med* 1996; **154**: 771–782.
48 Barnes PJ, Basbaum CB, Nadel JA, Roberts JM. Anatomy, pathology, and physiology of the tracheobronchial tree: emphasis on the distal airways. *Nature* 1982; **299**: 444–447.
49 Gelfland FW, Kraft M. The importance and features of distal airways in children and adults. *J Allergy Clin Immunol* 2009; **124**: S84–S87.
50 Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. *Eur Respir J* 1998; **12**: 1346–1353.
51 Van Schayck CP, Donnell D. The efficacy and safety of QVAR (hydrofluoroalkane-beclometasone dipropionate extrafine aerosol) in asthma (Part 2): clinical experience in children. *Int J Clin Pract* 2004; **58**: 786–794.
52 Van Aalderen WM, Price D, De Baets FM, Price J. Beclometasone dipropionate extrafine aerosol versus fluticasone propionate in children with asthma. *Respir Med* 2007; **101**: 1585–1593.
53 Van Aalderen WM, Grigg J, Colice G, Martin RJ, Roche N, Dorinsky P, *et al.* Real-world effectiveness of extrafine hydrofluoroalkane beclomethasone versus fluticasone propionate and inhaled corticosteroid/long acting beta-agonist as step-up therapy in paediatric asthma. CIPP XII 2013 Abstracts. Available from http://rirl.org/index.php?option=com_phocadownload&view=category&download=85:submission_comparing%20paediatric%20step-up%20therapies_sg14jan2013&id=1:public-downloads.
54 Agertoft L, Pedersen S. Importance of training for correct Turbuhaler use in preschool children. *Acta Paediatr* 1998; **87**: 842–847.
55 Tal A, Golan H, Grauer N, Aviram M, Albin D, Quastel MR. Deposition pattern of readiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in Young children with airway obstruction. *J Pediatr* 1996; **128**: 479–484.
56 Wildhaber JH, Dore N, Wilson JM, Devadason SG, le Souëf PN. Inhalation therapy in asthma: nebulizer or pressurised metered-dose inhaler with holding chamber? *In vivo* comparison of lung deposition in children. *J Pediatr* 1999; **135**: 28–33.