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. 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 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.

**INTRODUCTION**

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.
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

Consistency 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 ICSSs, 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 ICSSs 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.2 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; Clnil, 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.27–29 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.30–32 Another possibility in children 7 years or older and in adults is a breath-actuated device.31 Breast-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 ‘chamber’ increases drug delivery to where it is needed.33 Multiple breaths may also increase drug delivery into the airways. Schultz et al.24 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.23 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 or 41.8% in the older group inhaling 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.13,37 Most children aged 4 years or older (and sometimes even younger) can 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.

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

<table>
<thead>
<tr>
<th>Author/Journal</th>
<th>Age</th>
<th>Device</th>
<th>Breathing pattern</th>
<th>Drug</th>
<th>Mean lung deposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agertoft and Pedersen37</td>
<td>10–25 mo</td>
<td>Nebuhaler (750 ml), Babyspacer</td>
<td>30 s tidal breathing, 30 s tidal breathing</td>
<td>Budesonide</td>
<td>26.7% (17–44)</td>
</tr>
<tr>
<td>Arch Dis Child, 1994</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19.7% (9–33)</td>
</tr>
<tr>
<td>Tal et al56</td>
<td>0.25–5 y</td>
<td>pMDI-Aerocochamber</td>
<td>30 s tidal breathing</td>
<td>Salbutamol</td>
<td>1.97% (1.4)</td>
</tr>
<tr>
<td>J Pediatrics, 1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wildhaber et al.6,</td>
<td>2–4 y</td>
<td>pMDI- Aerocochamber</td>
<td>5 Tidal breaths</td>
<td>Salbutamol</td>
<td>5.4% (2.1)</td>
</tr>
<tr>
<td>J Pediatrics, 1999</td>
<td></td>
<td>in the 5–9-y group</td>
<td></td>
<td></td>
<td>9.6% (3.9)</td>
</tr>
<tr>
<td>Wildhaber et al.6,</td>
<td>&lt; 48 mo</td>
<td>Babyhaler</td>
<td>Tidal breathing</td>
<td>Sabutamol</td>
<td>16.4% (5.5)</td>
</tr>
<tr>
<td>J Pediatrics, 2000</td>
<td></td>
<td>Volumatic</td>
<td>Tidal breathing</td>
<td></td>
<td>28.2% (6.7)</td>
</tr>
<tr>
<td>Roller et al.20</td>
<td>5–7 y</td>
<td>Aerocochamber</td>
<td>Tidal breathing</td>
<td>Extra-fine HFA beclomethasone</td>
<td>35.4% (8.3)</td>
</tr>
<tr>
<td>Eur Respir J, 2007</td>
<td>8–10 y</td>
<td></td>
<td></td>
<td></td>
<td>47.5% (13.0)</td>
</tr>
<tr>
<td></td>
<td>11–17 y</td>
<td></td>
<td></td>
<td></td>
<td>54.9% (11.2)</td>
</tr>
<tr>
<td></td>
<td>5–7 y</td>
<td></td>
<td></td>
<td></td>
<td>58.1% (6.6)</td>
</tr>
<tr>
<td></td>
<td>8–10 y</td>
<td></td>
<td></td>
<td></td>
<td>56.6% (5.2)</td>
</tr>
<tr>
<td></td>
<td>11–17 y</td>
<td></td>
<td></td>
<td></td>
<td>58.4% (9.2)</td>
</tr>
<tr>
<td></td>
<td>2–7 y</td>
<td>Aerocochamber plus</td>
<td>2 Tidal breaths</td>
<td>Salbutamol</td>
<td>40% (95% CI: 34–46%)</td>
</tr>
<tr>
<td>Schulz et al.34</td>
<td></td>
<td></td>
<td>9 Tidal breaths</td>
<td></td>
<td>41% (95% CI: 36–47%)</td>
</tr>
<tr>
<td>Pediatrics, 2010</td>
<td></td>
<td></td>
<td>Funhaler</td>
<td></td>
<td>39% (95% CI: 34–43%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 Tidal breaths</td>
<td></td>
<td>38% (95% CI: 35–42%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Volumatic</td>
<td></td>
<td>37% (95% CI: 33–41%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9 Tidal breaths</td>
<td></td>
<td>43% (95% CI: 40–46%)</td>
</tr>
</tbody>
</table>

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.
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. in another study in which the breathing pattern of 4–8-year-old children was simulated, 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. 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. 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. 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.

### Table 2. Age indication of the different types of inhalers

<table>
<thead>
<tr>
<th></th>
<th>0-3 y</th>
<th>4-6 y</th>
<th>7 y and older</th>
</tr>
</thead>
<tbody>
<tr>
<td>pMDI</td>
<td>+ Spacer (small) with mask + Spacer (small) with mouth piece + Spacer with mouth piece</td>
<td>10 times tidal breathing 2 deep breaths 5–7 s breath-holding 1 deep breath 7 s breath-holding Quick and forcefully deep inhalation 5–7 s breath-holding</td>
<td>Dose indication of different inhaled corticosteroids</td>
</tr>
<tr>
<td>DPI</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BAI</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

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

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.

WHERE SHOULD INHALED CORTICOSTEROIDS AND β₂-AGONISTS BE DELIVERED?

The most important inhaled medicines for the treatment of asthma and early-childhood wheezing are β₂-adrenergic bronchodilators and ICSs. The inflammatory process involves the entire airway and, as corticosteroid receptor density increases in the peripheral airways, ICs delivery to small airways is important. As β₂ receptors are found equally in the large and smaller airways, targeting wide areas of the airways may be important for bronchodilators as well.

Small-particle ICSs, such as ultra-fine HydroFluoroAlkane BDP aerosol and ciclesonide, may offer a potential benefit in young children with smaller airways. 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.

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

Comparisons based on efficacy data. Doses according to GINA guidelines. Abbreviation: ICS, inhaled corticosteroid. Approved for once daily dosing in mild patients.
Inhaler choice for different children groups
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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. 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. 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 β₂-agonist.

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. 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 β₂-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 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 Smith 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, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Mundipharma, Medapharma, Novartis, Napp, Nycoderm, Pfizer, Sandoz and Teva. Consultancy: Almirall, Amgen, Astra Zeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Mundipharma, Medapharma, Novartis, Napp, Nycoderm, Pfizer, Sandoz and Teva. Grants/Grants Pending: UK National Health Service, Aerocrine, Astra Zeneca, Boehringer
Inhaler choice for different children groups

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Inhaler competence in asthma: common errors, barriers and technique through training.

GlaxoSmithKline, Chiesi, GlaxoSmithKline, Meda, Merck, Mundipharma, Novartis, Nycomed, Orion, Pfizer, Takeda, Teva and Zentiva. Payments for lectures/speaking: Almirall, AstraZeneca, Activaero, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Novartis, Medapharma, Merck, Mundipharma, Pfizer, SkyPharma, Takeda and Teva. Payment for manuscript preparation: Merck, Mundipharma and Teva. Patents (planned, pending or issued): AKL Ltd. Payment for the development of educational materials: GlaxoSmithKline. Stock/Stock options: Shares in AKL Ltd, which produces phytopharmaceuticals and owns 80% of Research in Real Life Ltd and its subsidiary social enterprise Optimum.

Patient Care. Payment for travel/accommodations/meeting expenses: Aerocline, Boehringer Ingelheim, Napp, Novartis, Mundipharma and Teva. Funding for patient enrolment or completion of research: Chiesi, Almirall, Zentiva and Teva.


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