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Paediatric pulmonary drug delivery: considerations in asthma treatment

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Aerosol therapy, the preferred route of administration for glucocorticosteroids and short-acting β_2-adrenergic agonists in the treatment of paediatric asthma, may be given via nebulisers, metered-dose inhalers and dry powder inhalers. For glucocorticosteroids, therapy with aerosolised medication results in higher concentrations of drug at the target organ with minimal systemic side effects compared with oral treatments. The dose of drug that reaches the airways in children with asthma is dependent on both the delivery device and patient-related factors. Factors that affect aerosol drug delivery are reviewed briefly. Advantages and disadvantages of each device and device-specific factors that influence patient preferences are examined. Although age-based device recommendations have been made, the optimal choice for drug delivery is the one that the patient or caregiver prefers to use, can use correctly and is most likely to use consistently.

Keywords: administration, asthma, device, dry powder inhaler, nebuliser, paediatrics, pressurised metered-dose inhaler, pulmonary

Expert Opin. Drug Deliv. (2005) 2(6):965-980

1. Introduction

Choosing a method of drug administration for children with airway disease is as critical as the choice of medication itself. Asthma medications may be administered orally or via inhalation. Oral administration of asthma medications is generally more convenient, portable and efficient than the use of an inhaler device. However, systemic exposure after oral administration of many asthma medications (e.g., oral glucocorticosteroids) is greater than that after topical drug administration, with a higher incidence of adverse events. In contrast, inhaled administration of asthma treatments results in higher concentrations of drug at the target organ, the lung, and minimises systemic adverse events [1,2].

The dose of drug that reaches the airways varies depending on the route of administration, the delivery device and the product formulation. Inhaler devices, many of which have been developed for adults, may be difficult for young children to use properly [1,3]. A less-than-optimal technique can result in decreased drug delivery and potentially reduced efficacy [4,5]. Unfortunately, improper inhalation technique is common [6-8]. Children and their families vary in physical and cognitive abilities, as well as in their willingness to adhere to therapy. Assessing desired convenience, physical coordination and willingness to learn new device techniques helps to ensure that the most suitable delivery device (i.e., one that the patient or caregiver prefers to use, can use correctly and is most likely to use consistently) is chosen for each patient. However, even in patients that adhere to a particular regimen, the benefit from inhaled therapy may not be observed if they cannot use the prescribed device correctly (lack of competence), or if they choose to use it in an inappropriate manner (contrivance) [9].

Table 1. Available delivery devices for inhaled asthma medications [1].

Delivery device	Medication	Recommended age for use*	Remarks
pMDI	Anticholinergics, β_2-agonists, corticosteroids, cromolyn sodium, nedocromil sodium	> 5 years (< 5 years with spacer/holding chamber and face mask for some children)	The child may have difficulty triggering a puff while inhaling; helps to use device with a spacer/holding chamber
Breath-actuated MDI	β_2-Agonists	> 5 years	The child may not be able to generate the necessary inspiratory flow; device does not require the use of a holding chamber or spacer
Dry powder inhaler	β_2-Agonists, corticosteroids	> 5 years (can be used in 4 year olds but delivery is more consistent at > 5 years of age)	Some devices deliver drug more effectively than an MDI; some devices may not work in children with low inspiratory volumes
Nebuliser	Anticholinergics, β_2-agonists, corticosteroids, cromolyn sodium	Patients of any age who cannot use an MDI with spacer/holding chamber or with face mask	Useful in infants and very young children, and in any child with a moderate-to-severe asthma episode, although MDI with spacer/holding chamber may be as effective; delivery method of choice for cromolyn sodium

*Suggested ages; clinicians should use their own judgement to tailor treatment according to the specific needs and circumstances of the individual child or family.
MDI: Metered dose inhaler; pMDI: Pressurised metered-dose inhaler.

2. Guideline recommendations

Medications used to reverse and prevent the symptoms of asthma include controllers, which are administered chronically to treat persistent asthma, and relievers, which are used as needed to relieve acute symptoms, such as wheezing, chest tightness and cough [10]. Controllers have also been described as prophylactic or maintenance medications, and relievers are often referred to as rescue medications or quick-relief medicines [10]. Short-acting β_2-adrenergic agonists (SABAs) are preferred for relief of symptoms and are the only medication recommended for mild intermittent asthma [10]. So far, the most effective, single-medication controllers are inhaled glucocorticosteroids (ICSs), which are the preferred therapy for mild persistent asthma [10]. For patients whose asthma is inadequately controlled with ICSs alone, inhaled long-acting β_2-adrenergic agonists (LABAs), such as salmeterol and formoterol, are indicated as adjunct daily therapy [10]. Combination ICS/LABA inhaler devices are available for patients with moderate or severe persistent asthma and who require dual-agent therapy for daily disease control [1].

2.1 Age-based device recommendations

Current guidelines for the selection of asthma inhaler devices are inconsistent and are not evidence based [11]. Recent evidence-based guidelines from the American College of Chest Physicians (ACCP) and the American College of Asthma, Allergy and Immunology (ACAAI), which systematically reviewed the efficacy of bronchodilator and ICS devices in asthma, concluded that all devices can be equally efficacious [12]. The American Academy of Allergy, Asthma & Immunology (AAAAI) has developed specific guidance regarding the choice of inhalation devices for paediatric asthma patients (Table 1) [1]. Although age-related suggestions are made regarding the most suitable devices, these guidelines encourage clinicians to use their own judgement and consider the needs of the individual child and family when making device recommendations. Examples of the different types of aerosol devices are illustrated in Figure 1. In children younger than 2 years, the AAAAI recommends the use of a nebuliser with face mask or a pressurised metered-dose inhaler (pMDI) with a spacer/holding chamber and face mask. Clinicians are cautioned against use of the 'blow-by' technique (the administration of medication by holding a mouthpiece or tubing near the nose and mouth without a proper mask) because it decreases lung deposition [1]. Children of 3 – 5 years of age may be able to use a pMDI with spacer/holding chamber. However, if desired therapeutic effects are not achieved or if the child cannot properly use this device, a nebuliser or a pMDI plus spacer/holding chamber with face mask may be required [1].

For school-aged children, AAAAI recommends MDIs, dry powder inhalers (DPIs) or nebulisers [1]. Importantly, children must be able to produce the necessary inspiratory effort and coordination for the chosen device [1]. Furthermore, clinicians should consider school medication policies and tailor their recommendations if necessary [1]. ICSs and other inhaler controller therapies that have been approved by the US FDA for children with asthma and are shown in Figure 2. Nebulised

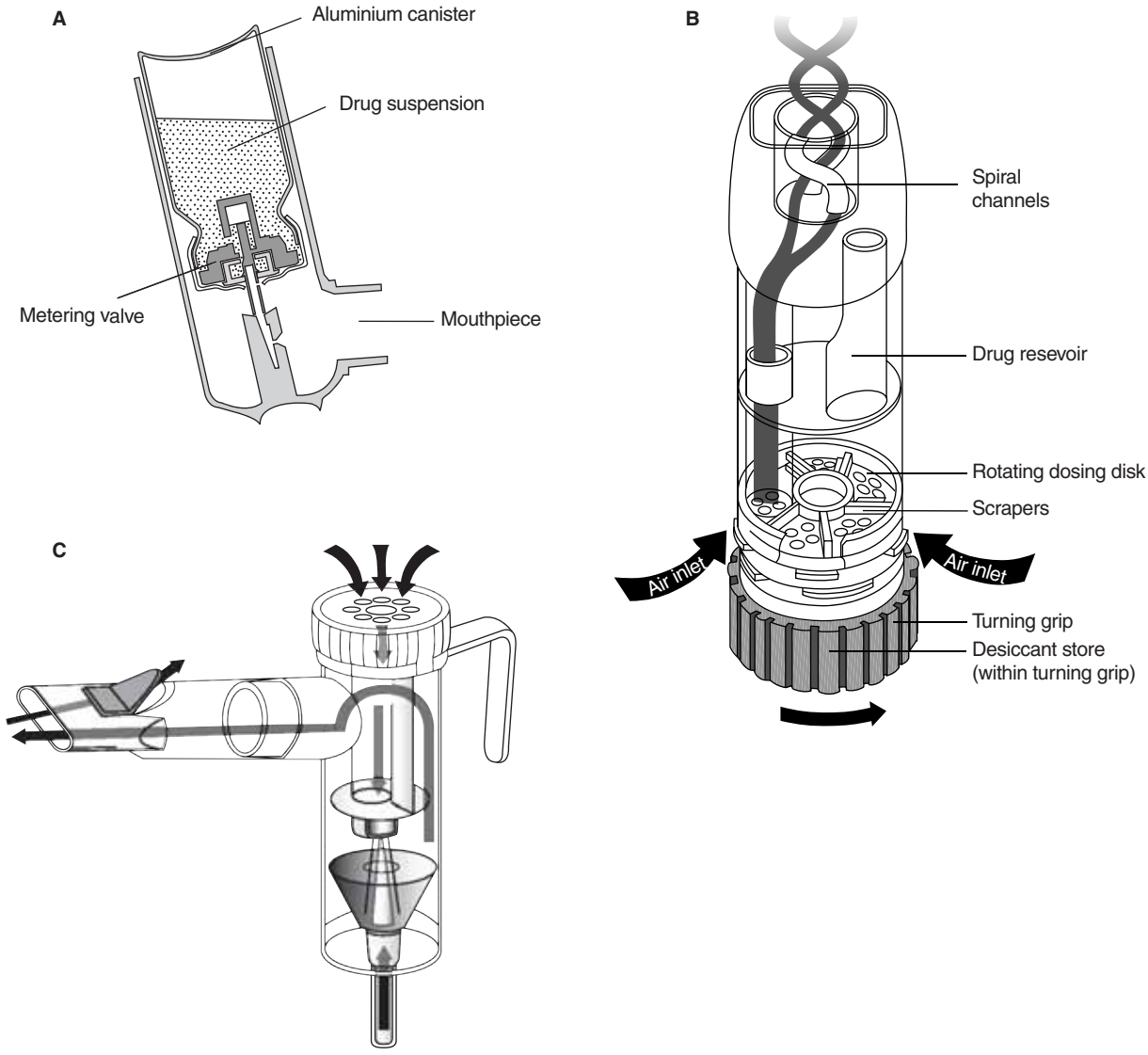

Figure 1. Types of aerosol devices include A. pressurised metered-dose inhalers (with and without holding chambers and spacers); B. dry powder inhalers (single capsules, multi-dose disks and multi-dose reservoirs); and C. nebulisers (jet and ultrasonic). A. Reproduced with permission from O'CALLAGHAN C, WRIGHT P: In: *Drug Delivery to the Lung*. Marcel Dekker, New York, NY, USA (2001) 162:337-370. [13]; B. Reproduced with permission of AstraZeneca; C. Reproduced with permission of PARI Respiratory Equipment, Inc.

cromolyn and nebulised budesonide are the only controller medications indicated for ages 1 – 4 years based on adequate efficacy and safety studies.

Guidelines from the Global Initiative for Asthma (GINA), a collaboration between the National Heart, Lung and Blood Institute (US) and the World Health Organization [10], recommend a pMDI with spacer plus face mask for infants and preschool children, a pMDI with spacer plus mouthpiece for children 4 – 6 years of age, and a DPI, breath-actuated pMDI or pMDI with spacer for children 6 years and older [10]. These guidelines recommend a nebuliser with face mask as an alternative for children 6 years and younger and a nebuliser with a mouthpiece as an alternative for those older than 6 years.

3. Factors affecting drug delivery to the lung

Drug deposition in the lung varies according to a number of factors, including the size and speed of the particles emitted from the inhalation device and the skill level and technique used by the patient to administer treatment [6,9,14]. Efficient delivery of drug to the lung depends on optimal particle size. An ideal inhalation device emits a precise and uniform dose of respirable particles [15] and can be used with ease on a long-term basis.

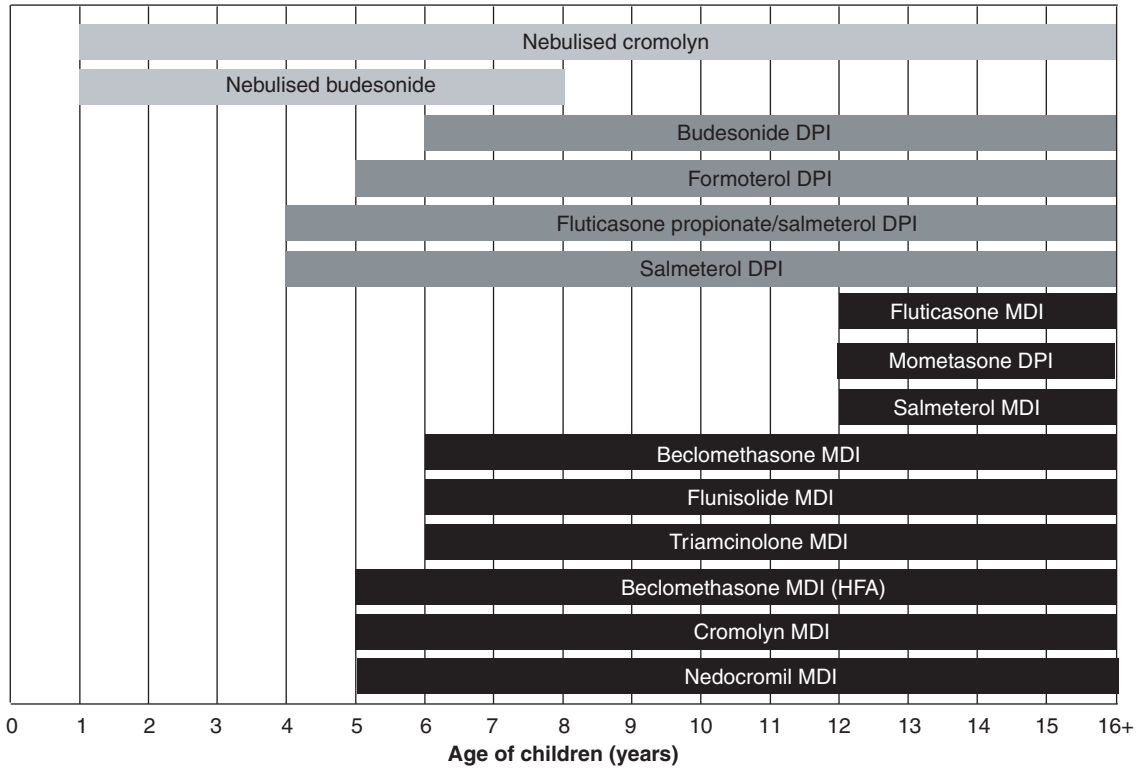

Figure 2. Age-specific indications of the US FDA for use of controller and reliever medications administered via nebuliser, MDI or DPI in children.

DPI: Dry powder inhaler; HFA: Hydrofluoroalkane; MDI: Metered-dose inhaler.

3.1 Particle size and deposition

Particles from 1 to 5 µm in diameter are generally considered within the respirable range because they bypass immunological defence mechanisms that protect the lungs from foreign materials. They also tend to reach the lower airway and deposit in the lungs before they are exhaled [16,17]. Particles of < 0.3 and 0.6 µm in size are often exhaled because they are too small to be deposited in the airways by gravity [18]. Particles of > 5 µm in size are more likely to be deposited in the upper airway and be swallowed [2,17].

One meta-analysis of deposition studies of nebulised drugs reported that particle size was inversely correlated with lung deposition [19]. Because different particle sizes of the same therapeutic agent can affect efficacy of an inhaled medication, measurement of particle size has become an important part of product development and quality control of currently marketed products [17].

The size of the particle influences the mechanism of lung deposition in infants and small children [20]. Because the upper and lower airway diameters of infants and children are small, the majority of particles that are > 3 µm are influenced by inertial force, depositing in the upper airway following impact. Because inertial impaction is flow dependent, slowing inspiratory flow permits large particles to pass through the upper airways and into the lungs. For particles that are < 2 µm and larger particles under low-flow conditions, the force of gravity leads to sedimentation of particles in the lung. As the residence time of particles in the lung increases, the probability of lung deposition increases. Finally, particles that diffuse are those so small that their movement is influenced more by Brownian motion than gravity [20].

3.2 Patient characteristics

Anatomical, physiological, cognitive and emotional differences may create challenges in the use of inhalation devices in young children [16]. For example, the inability of patients to coordinate inhalation with actuation of a pMDI has been reported to result in the deposition of drug in the oropharynx [21]. Because children have less developed coordination skills than adults, they may benefit from the routine use of pMDIs with spacers or holding chambers, or nebulisers.

Compared with adults, infants have low tidal volumes, small vital capacity, small functional residual capacity and a short respiratory cycle. As a result, the pulmonary deposition of aerosol particles is hampered by a short residence time in the airways [20,22]. Furthermore, because young children have small airways and rapid respiration, they are unable to hold their breath with inhaled medication. Nasal breathing among infants or young children wearing face masks can also result in the loss of drug particles [23]. Other important factors to consider include the

Table 2. Advantages and disadvantages of each type of aerosol-generating device or system clinically available [12].

Type	Advantages	Disadvantages
Small-volume jet nebuliser	Patient coordination not required Effective with tidal breathing High dose possible Dose modification possible No CFC release Can be used with supplemental oxygen Can deliver combination therapies if compatible	Lack of portability Pressurised gas source required Lengthy treatment time Device cleaning required Contamination possible Not all medication available in solution form Does not aerosolise suspensions well Device preparation required Performance variability Expensive when compressor added in
Ultrasonic nebuliser	Patient coordination not required High dose possible Dose modification possible No CFC release Small dead volume Quiet Newer designs small and portable Faster delivery than jet nebuliser No drug loss during exhalation (breath-actuated devices)	Expensive Need for electrical power source (wall outlet or batteries) Contamination possible Not all medication available in solution form Device preparation required before treatment Does not nebulise suspensions well Possible drug degradation Potential for airway irritation with some drugs
pMDI	Portable and compact Treatment time is short No drug preparation is required No contamination of contents Dose–dose reproducibility high Some can be used with breath-actuated mouthpiece	Coordination of breathing and actuation needed Device actuation required High pharyngeal deposition Upper limit to unit dose content Remaining doses difficult to determine Potential for abuse Not all medications available Many use CFC propellants in US
Holding chamber, reverse-flow spacer, or spacer	Reduces need for patient coordination Reduces pharyngeal deposition	Inhalation can be more complex for some patients Can reduce dose available if not used properly More expensive than MDI alone Less portable than MDI alone Integral actuator devices may alter aerosol properties compared with native actuator
DPI	Breath actuated Less patient coordination required Propellant not required Small and portable Short treatment time Dose counters in most newer designs	Requires moderate to high inspiratory flow Some units are single dose Can result in high pharyngeal deposition Not all medications available

CFC: Chlorofluorocarbon; DPI: Dry powder inhaler; MDI: Metered-dose inhaler; pMDI: Pressurised metered-dose inhaler.

Reproduced with permission from DOLOVICH MB, AHRENS RC, HESS DR *et al.*: Device selection and outcomes of aerosol therapy: evidence-based guidelines. *Chest* (2005) **127**:335-371 [12].

aversions that some children have to face masks and the impact of fussiness or crying on aerosol delivery.

3.3 Device characteristics

To overcome the challenges of delivering inhalation therapy in children, a number of devices have become available, including pressure-driven and ultrasonic nebulisers, and simple tubes or valved holding chambers to optimise drug delivery [2]. Pulmonary delivery varies with device and formulation. Ensuring optimal drug delivery requires that the most appropriate device type be chosen according to individual patient factors. Although all delivery devices are similar with regard to efficacy, each device has its advantages and disadvantages (Table 2) [12].

4. Nebulisers

Nebulisers are used to reduce liquid medication to an extremely fine cloud or mist. Nebuliser devices include conventional jet nebulisers, ultrasonic nebulisers, open-vent nebulisers, breath-assisted open-vent nebulisers and adaptive aerosol delivery devices [24]. Most nebulisers use compressed air to create an aerosol; however, some use ultrasonic energy [24]. Jet nebulisers use compressed gas driven through a narrow

hole (the venturi) to atomise liquid in the drug reservoir; larger particles fall back into the reservoir or are deflected by baffles that reduce particle size. Ultrasonic devices contain a piezoelectric crystal, which vibrates to create a high-frequency sound wave that produces the aerosol particles [24,25]. The use of ultrasonic nebulisers is not recommended with highly viscous solutions or suspensions because these formulations reduce the propagation of ultrasonic waves, thus decreasing output [25]. Open-vent nebulisers incorporate an extra vent into the system, resulting in continuous greater airflow and shorter nebulisation times. Breath-assisted open-vent nebulisers were designed to overcome aerosol loss during exhalation; however, because they are dependent on inspiratory flow, further studies are needed before they are recommended for use in young children and infants [24]. Adaptive aerosol nebulisers deliver doses that are independent of breathing pattern, but these devices are expensive [24]. The newest nebuliser devices use a vibrating mesh or plate to generate a fine-particle, low-velocity mist. Advantages of vibrating plate technology include portability, battery operation, efficiency of delivering aerosols and suspensions, and minimal residual volume of medication in the device [26].

Although nebulisers are an appropriate device for young children and infants [12], these devices may be cumbersome and time consuming if not used correctly. Mixing multiple nebulised asthma medications results in larger volume, which needlessly increases nebulisation time [27,28]. In most cases, it is faster to administer each drug individually. Many families of young children prefer to use a nebuliser in conjunction with a distraction technique, such as a video [29]. Nebulisers offer several key advantages, such as no requirement for hand–inspiratory coordination, convenience in acute asthma attacks, and ease of use in sleeping infants and in sick children [24,30].

4.1 Controllable factors affecting delivery of nebulised drugs

As described in the following sections, nebuliser function may be influenced by several factors that can be controlled by the physician or caregiver. In addition to nebuliser design, drug delivery from these devices is dependent on the gas flow to power the nebuliser, residual volume of drug, volume fill and various patient-specific factors.

4.1.1 *Inherent characteristics of nebuliser systems*

The efficient delivery of nebulised medication requires a low-cost device that consistently delivers a sufficient amount of drug within a short period of time with minimal waste [31]. Currently, design differences among the many marketed devices can result in varying degrees of drug delivery to the patient. Inherent device characteristics affecting nebuliser output include driving gas flow, residual volume of drug and volume fill (Figure 3) [31,32]. For example, nebulisation time may be decreased by increasing the driving gas flow through jet nebulisers to increase drug output and reduce particle size [31]. Optimum flow is often from 6 to 10 l/min; however, flow depends on the nebuliser and drug used. When open-vent nebulisers are used, a high-driving gas flow may not be as important because the extra opening provides greater overall airflow in the nebulisation chamber [31]. A greater proportion of drug is nebulised by increasing volume fill or decreasing residual volume, but these factors increase nebulisation time [31].

Because of the extreme variability in nebuliser system performance, the therapeutic effects of a drug depend, in part, on the choice of nebuliser [25]. One study compared nebuliser/compressor combinations to assess their efficiency in the delivery of budesonide inhalation suspension (Table 3). The performance among various nebuliser/compressor combinations varied widely. One of the most efficient systems tested was the commercial system, the PARI LC-Jet Plus™/PARI Master compressor [33].

An earlier study that tested albuterol delivery among 17 different jet nebuliser systems reported that respirable fraction was from 22 – 72%, and time to nebulise ranged from 2.3 – 21 min [34]. The optimal devices in the albuterol study were breath-enhanced nebulisers (PARI Jet®, PARI LC-Jet and Sidestream®).

4.1.2 *Patient factors*

Face mask seal and patient factors, such as tidal volume, breathing pattern, nose breathing and crying, affect the efficiency of nebulised drug delivery [16,24,35]. In older children, tidal inspiratory flow is higher than nebuliser output, so the aerosol is diluted by entrained air. In infants younger than 6 months, inspiratory flow is lower than nebuliser output; therefore, these patients receive undiluted aerosol [24]. Nevertheless, because infants younger than 6 months have low inspiratory flow and a low inspiratory–expiratory ratio, they inhale less aerosol compared with a larger child or adult [22].

Young children and infants frequently try to escape the face mask, which decreases drug delivery by causing the seal between the face and the mask to be broken intermittently or continuously [32,36]. Thus, the face mask should be applied firmly to optimise drug delivery. Although very young infants do not react adversely when the face mask is applied, infants aged 6 – 9 months frequently become distressed when a face mask is applied; this type of reaction often peaks by 2 years of age. By 2.5 or 3 years of age, children are more likely to cooperate and they become interested in self-administering the medication [16].

When the duration of nebulisation is long, the child may be less likely to consistently take deep breaths, which allows maximal delivery of the aerosol to the lower lung [20]. Delivery of medication is most efficient during quiet inhalation; almost no medication is deposited into the lungs of a crying infant or child [20,35,37]. One study that examined urinary excretion of nebulised sodium cromoglicate in 17 infants reported that 0.43% of the dose was excreted in the urine of settled infants compared with 0.11% of the dose in crying infants [35]. These results disproved the commonly held belief that crying children inhale a greater proportion of the administered dose [35].

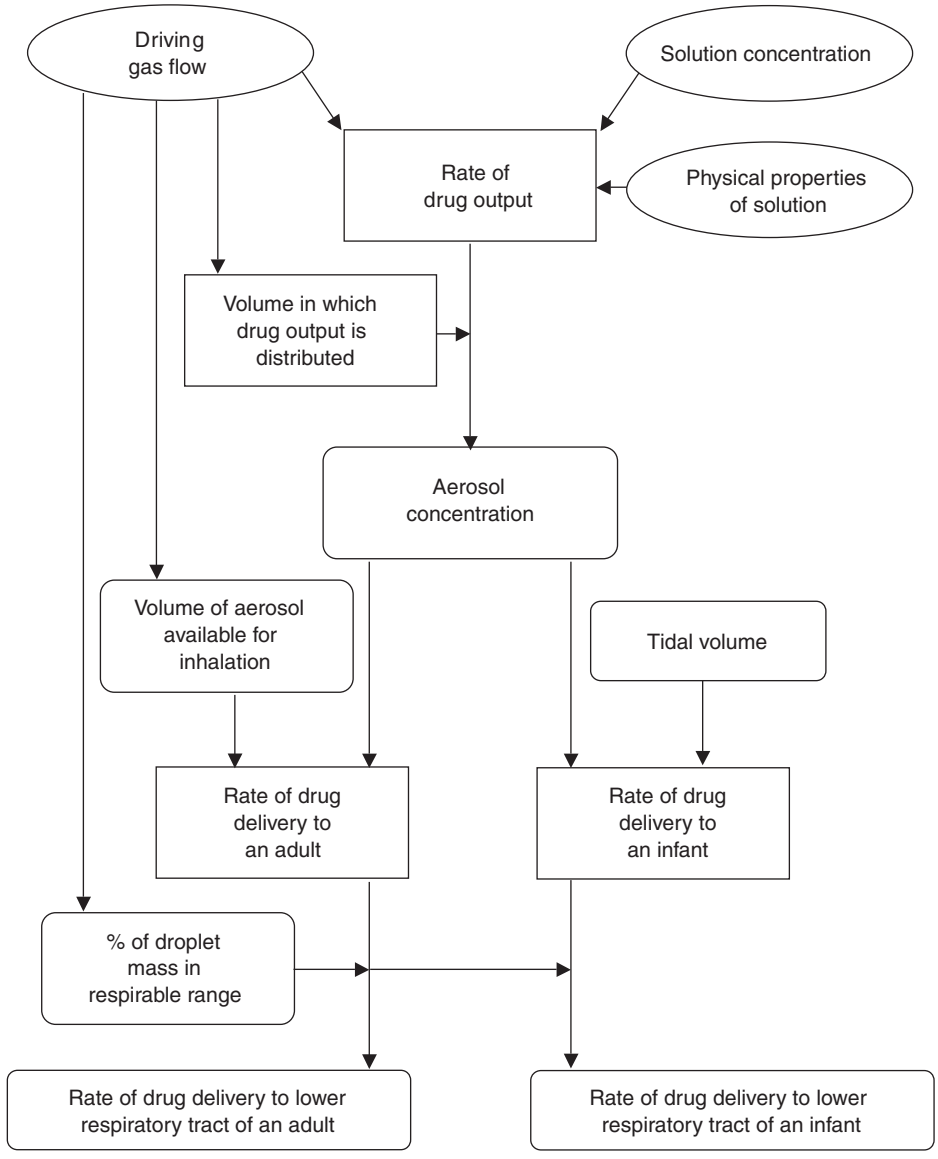

Figure 3. This diagram illustrates the complex interaction of technical factors that influence drug delivery from a jet nebuliser to the patient. Reproduced with permission from EVERARD ML, CLARK AR, MILNER AD: Drug delivery from jet nebulisers. *Arch. Dis. Child.* (1992) **67**:586-591 [32].

During crying, a very long exhalation is followed by a rapid and brief inhalation. Medication is not available during exhalation, and the inertia of the inhaled medication during very fast inhalation probably results in deposition of medication in the oropharynx instead of the airways [20]. Therefore, whenever possible, aerosolised drugs should be administered when children are quiet or sleeping. However, because many children awaken as soon as the mask is applied, caregivers should be counselled on distraction strategies, such as administering therapy while the child is watching a video, to minimise distress and promote tidal breathing [16]. Maximising the efficiency of aerosol delivery from a nebuliser involves slow tidal breathing with occasional deep breaths, as well as the use of a mouthpiece or tightly fitting mask [30].

The face mask seal is critical for efficient delivery of medications. In a model simulating a respiratory pattern of 32 breaths/min with a tidal volume equivalent to that of a 9-month-old infant (50 ml), deposition of sodium cromoglicate via a Cirrhus jet nebuliser (Intersurgical) was decreased by ~ 60 and 85%, when the mask was held 1 and 2 cm, respectively, from the model face [32]. Using the Sophia Anatomical

Table 3. Delivery times for nebulised budesonide by nebuliser–compressor model.

Nebuliser + compressor	Time to dryness (min)
PARI LC-Jet Plus + PARI Master	≤ 5.0
PARI LC-Jet Plus + DeVilbiss Pulmo-Aide	≤ 5.0
PARI LC-Jet + PARI Master	≤ 5.0
PARI LC-Jet + DeVilbiss Pulmo-Aide	≤ 5.0
Hudson Updraft II NEB-U-MIST + Hudson	6.8
DeVilbiss Pulmo-Neb + DeVilbiss Pulmo-Aide	7.2
Hudson AVA-Neb + Hudson	7.8
Hudson AVA-NEB + DeVilbiss Pulmo-Aide	8.1
Hudson Updraft II NEB-U-MIST + DeVilbiss Pulmo-Aide	10.8

Reproduced with permission from SMALDONE GC, CRUZ-RIVERA M, NIKANDER K: *In vitro* determination of inhaled mass and particle distribution for budesonide nebulizing suspension. *J. Aerosol. Med.* (1998) **11**:113-125 [33].

Infant Nose–Throat (SAINT) anatomically correct model of the upper airway of a 9-month-old, nose-breathing infant, Geller *et al.* demonstrated that use of the blow-by technique (1.5 cm from the face) decreased lung deposition of budesonide by as much as 43% [38].

4.2 Paediatric lung deposition in nebuliser studies

Data on lung deposition in infants and young children are limited, partly because of ethical concerns regarding the use of radiolabelled aerosols in this population [22]. The existing data suggest that the pulmonary deposition of nebulised aerosols in children may be < 1% of the nominal dose, compared with 8 – 22% in adults [16,39]. However, in spite of the low efficiency of deposition, children typically receive weight-appropriate doses. For example, 0.5% of a 2500-µg dose of albuterol provides a pulmonary dose of 12.5 µg, or 6.25 µg/kg in a 2-kg infant, whereas 10% lung deposition provides a 250-µg dose, or 3.6 µg/kg for a 70-kg adult [22].

A pharmacokinetic study of budesonide administered via a widely used jet nebuliser (PARI LC-Jet Plus) reported that the systemic availability of budesonide in young children was 6%, which is half the rate of that previously reported in healthy adults (13%) who used the same nebuliser [40]. The authors suggested that this estimate of lung deposition was probably close to the maximum that could be achieved with the nebuliser used, as this study used a mouthpiece instead of a face mask to administer treatment. The use of face masks often results in nose breathing, which reduces the lung dose [41,42]. However, in a comparative study involving infants and young children, no differences in clinical efficacy were reported when budesonide was administered via the PARI LC-Jet Plus with a face mask versus a mouthpiece [43].

5. Metered-dose inhalers

A pMDI contains three major components: a reservoir that contains drug in liquefied gas propellant, a metering valve that delivers a known volume of drug when depressed and a spray actuator. Typically, a pMDI contains drug substance, up to three different propellants and one or more surfactants or lubricants [13]. In response to the 1987 Montreal protocol, the propellant chlorofluorocarbon is being replaced with hydrofluoroalkane 1,1,1,2-tetrafluoroethane [13].

Pressurised MDIs are efficient, delivering medication in a short period of time, small and highly portable [12,44]. However, there are several drawbacks to the use of pMDIs, including the need for coordination of breathing with actuation, which can be difficult in young children. In addition, when pMDIs are not used with a spacer or holding chamber, the high aerosol velocity leads to oropharyngeal deposition. It is also difficult to determine the number of remaining doses after continuous pMDI use in the absence of a dose counter.

Because pMDIs are so popular, various modifications have been made to enhance drug delivery. One such improvement is the introduction of breath-enhanced devices, which may become more popular than standard models. However, there are limited data on these devices at this time [13].

5.1 Factors affecting drug delivery from pMDIs

Poor technique is common in children using pMDIs [8]. Because the aerosol cloud leaves the canister of the pMDI at a very high speed, spacers and holding chambers may be used to overcome this challenge. The use of a spacer results in deceleration and maturation of the aerosol, whereas the use of a holding chamber, which is a valved spacer, permits breathing from a standing cloud of aerosol [21]. Delivery of drug from a spacer depends on the volume and shape of the spacer, the spacer valves, the spacer material and the use of detergent to reduce the electrostatic charge [21,45]. In addition to reducing problems with pMDI coordination and inhalation, spacers reduce adverse events of ICSs, such as oral candida, dysphonia, reflex cough and bronchospasm, by reducing oropharyngeal contact time [1,14]. Current recommendations support the routine use of a spacer device or holding chamber

when a pMDI is used to administer inhaled medications, regardless of patient age [1,10,12].

One study reported that 33% of children that used pMDIs with spacers did not correctly perform all the necessary steps despite previous instruction on proper use. The most common errors included not shaking the inhaler before use, not placing the mouthpiece between the teeth and lips, and not checking to see if the spacer valve was moving [8]. Of note, a significantly ($p = 0.02$) greater number of patients that received instructions at the pharmacy were able to perform all essential steps correctly compared with those who received instructions by their physicians [8]. Another study by these investigators demonstrated that repeated instruction sessions and demonstration of inhaler use during these sessions increases the ability of the child to use a pMDI with a spacer correctly [46]. Therefore, it is important to check inhalation technique periodically during follow-up visits.

Incorrect use of holding chambers, such as placing multiple puffs in a chamber or waiting too long between pMDI actuation and inhalation, has been reported to reduce drug delivery [12,47-50]. An *in vitro* study demonstrated that delaying inhalation by 5 s after actuation of a pMDI with spacer significantly ($p < 0.0001$) decreased drug recovery by ~ 30 – 60% [50]. Static charge also may decrease dose delivery because it accumulates on the walls of polycarbonate spacers and attracts drug particles [50]. Finally, an *in vitro* study that evaluated three different spacers reported that low flow reduced the total recovery of salmeterol from the Babyhaler®, but not with the Volumatic® or AeroChamber®. Therefore, low flow may not affect the delivery of drugs from most spacers [50].

Optimally, a spacer for young children would be intermediate in size so that the chamber could be emptied in a few breaths (but not so small that most of the delivered dose impacts on the spacer walls), be constructed of non-electrostatic material, contain an efficient one-way valve to accommodate the shallow breathing of a young baby, have minimal dead space in the valve and face mask, have a long half-life of drug in the chamber and have a tight-fitting face mask. Unfortunately, this type of spacer is not yet available [21]. However, optimal use of spacer devices can improve pulmonary delivery of the aerosol. For example, use of a detergent coating reduces the electrostatic charge on plastic spacers and improves drug delivery [45]. This process requires washing of the spacer in a diluted detergent solution and air drying. Moreover, physicians should become familiar and comfortable with one or two of the various spacers that are available and teach their patients proper use of one device. Switching between spacers is not recommended and may impact drug delivery.

In children younger than 2 years and in those aged 3 – 5 years who cannot use a pMDI with spacer alone, a face mask is recommended [1]. It is essential to ensure that the face mask seal is tight because holding the face mask even a small distance away from the face greatly reduces the amount of drug inhaled. Amirav and Newhouse conducted an *in vitro* study to evaluate the effect of varying the distance of the mask from the face on drug delivery, and an *in vivo* study to assess face mask leakage. Ventilation through the face mask was significantly reduced when the seal was not tight, with the *in vitro* component of the investigation demonstrating that with a positive linear relationship ($r = 0.55$; $p = 0.004$) between ventilation and the delivered dose of albuterol [36]. *In vivo*, ventilatory volumes increased significantly after parents ($n = 30$) were coached to hold the mask tightly against the child's face [36]. However, only 3 of the 10 children younger than 2 years reasonably cooperated; the others could not remain still for 12 – 15 s [36]. The variability of ventilation through the masks (Hans Rudolph, NebuChamber®, AeroChamber, Babyhaler) was remarkably high, even when the same device was used by the same patient [36]. For young patients who are unable to cooperate with the pMDI/spacer and face mask delivery system, an alternative may be administration during sleep. In an *in vitro* study that simulated the respiratory patterns of infants during sleep and whilst awake, lung doses of budesonide administered via the metal Nebuchamber with attached face mask were higher during simulated sleep breathing patterns than with waking respiratory patterns [51]. Although the clinical relevance of this finding requires further investigation, the administration of inhaled drugs during sleep may be an effective alternative for these children.

5.2 Lung deposition by pMDI

Data describing lung deposition following dosing from pMDIs have been reported from *in vivo* and *in vitro* filter-dose studies of ICSs and one imaging study that used radiolabelled salbutamol in young children [45,52,53]. The mean percentage of salbutamol administered via pMDI with spacer and AeroChamber deposited in the lungs of children 2.5 months to 5 years of age was 1.97 ± 1.4%. Airway deposition was not influenced by age, weight or respiratory rate [53].

One *in vivo* study compared lung doses of budesonide 400 µg administered via pMDI with NebuChamber and fluticasone 500 µg delivered via pMDI with Babyhaler amongst four age groups (1 – 2 months; 2 – 3 years; 4 – 6 years; 10 – 15 years). All children except the 1- to 2-month-old infants had asthma. The two youngest groups used only a face mask, whereas the oldest group used only a mouthpiece [52]. Children aged 4 – 6 years used both attachments. The percentage of the nominal dose of budesonide delivered from the NebuChamber was higher than that from fluticasone Babyhaler ($p = 0.002$) in all but the oldest age group, where results were similar between the devices [52]. Amongst those aged 4 – 6 years, use of a mouthpiece decreased the percentage of the nominal dose delivered to the filter compared with use of a face mask, which is in contrast to findings from nebuliser studies [52]. As expected, filter dose increased significantly ($p < 0.0001$) with age in both the NebuChamber and Babyhaler groups [52].

Another study used a model of a 9-month-old infant to compare lung doses of ICS formulations administered via pMDI with their respective spacers (budesonide with the NebuChamber and fluticasone hydrofluoroalkane with

Babyhaler) or with the AeroChamber, a general purpose spacer [45]. Overall, doses of fluticasone were significantly greater than those of budesonide regardless of which spacer was used. However, in children with a tidal volume < 50 ml, the choice of spacer became important, with the NebuChamber and AeroChamber yielding more favourable results than the Babyhaler.

6. Dry powder inhalers

Modern DPIs have been designed to deliver multiple doses of drug over a prolonged period of time. Unlike pMDIs, they do not contain chlorofluorocarbons, although they do contain indicator/warning systems that signal when the drug is close to depletion [54]. For some patients, DPIs may be easier to use than pMDIs because they are breath-actuated; there is no need to coordinate actuation with inhalation [54]. Furthermore, like pMDIs, they are small, portable and can deliver medication quickly. At present, all DPIs have been designed to rely on the inspiratory effort of the patient to lift the powder from the drug reservoir, dosing disk and so on. This requires a young child to reproduce a forceful inspiratory effort (> 30 l/min) [44,54].

DPI devices are increasingly used for the concurrent administration of ICSs and LABAs. With the advent of combination inhalers, clinicians are able to conveniently provide daily LABA therapy to patients whose asthma is inadequately controlled with low-to-medium dose ICSs alone. The LABAs salmeterol and formoterol are available as single-agent dry powder formulations and, depending on the country, as combination DPIs with fluticasone or budesonide, respectively [1]. Combination DPIs have the advantages and disadvantages of standard DPI devices with the added benefit of providing dual controller therapy in a single delivery device.

6.1 Considerations in DPI lung delivery in children

When inhaling medication from a DPI, the major differences between adults and children include inhaled volume and the peak inspiratory flow (PIF) [54]. However, the smaller inhaled volume in children is not an important determinant of efficacy, as the dose from a DPI has been shown to leave the device within the first few hundred millilitres of inhaled air, before the PIF is reached [55]. Furthermore, when children have been well trained in inhalation technique, they are able to achieve adequate PIF. In one study of the Turbuhaler®, following both individual and home training, the majority of children older than 4 years were able to produce PIF rates of ~ 55 l/min [56]. Studies have reported that PIF increases with age [57,58].

The effect of PIF on efficacy has been investigated in several studies. A study of the salbutamol Rotahaler® demonstrated that in children aged 7 – 14 years, improvement in forced expiratory volume in 1 s (FEV_1) was significantly greater ($p < 0.01$) when the inhalation was fast (90 – 120 l/min) or medium (60 – 80 l/min) compared with when inhalation was slow (30 – 50 l/min) [59]. Another study evaluated the relationship between clinical outcome and four different flow rates (13, 22, 31 and 60 l/min) when terbutaline was administered with the Turbuhaler to 14 children (7 – 15 years of age) with asthma [60]. Even the smallest PIF (13 l/min) increased FEV_1; progressive increases were observed with each increase of PIF (22 and 31 l/min) with the exception of the highest PIF (60 l/min), which was not associated with a further increase in FEV_1 [60]. However, because further dosing of terbutaline (1 mg) revealed further increases in FEV_1 at each PIF, the lack of difference observed between the 31- and 60-l/min PIFs was not attributed to a plateau effect [60].

PIF also was evaluated in a randomised, double-blind, placebo-controlled, crossover study amongst 18 children (8 – 15 years old) with exercise-induced asthma who used the Diskus® [57]. In this study, 50-µg doses of salmeterol were administered at two different PIFs (30 and 90 l/min), and falling FEV_1 was used as the primary outcome measure. At 1 and 12 h after dosing, no differences in FEV_1 were observed between the low- and high-flow salmeterol treatments during exercise challenge [57].

6.2 Lung deposition from DPI

In vitro data comparing the fine particle dose (i.e., < 5 µm) of budesonide Turbuhaler and fluticasone Diskhaler®/Diskus demonstrated that at equal levels of inspiratory force, Turbuhaler delivered the highest proportion of nominal dose as fine particles. During moderate inspiratory force, the fine particle dose was 45% of the Turbuhaler nominal dose and 13% of the Diskhaler nominal dose [61].

A paediatric *in vitro* study of budesonide Turbuhaler and fluticasone Diskus compared lung deposition from the devices by recording inhalation profiles of children with asthma and replicating these profiles with an electronic simulator to measure the emitted doses [55]. The fine and very fine particle fractions were significantly greater in the older children (8 year olds) than in the younger children (4 year olds). Furthermore, Turbuhaler delivered a substantially greater percentage of particles within the respirable range (i.e., fine and very fine particles) in both age groups compared with fluticasone Diskus (Figure 4) [55].

The only known *in vivo* comparison of the two most widely used DPIs in children, budesonide Turbuhaler and fluticasone Diskus, estimated lung deposition by determining the fraction of drug that was systemically absorbed from the lungs [62]. After Turbuhaler administration, absolute bioavailability of drug was almost four-times greater than that after Diskus administration (Figure 5) [62]. Furthermore, the coefficient of variation of lung deposition was more than twice as high in children who received fluticasone Diskus (61.2%) compared with that of children who received budesonide Turbuhaler (24.2%).

7. Comparisons of delivery devices for paediatric asthma

There are no known *in vivo* studies that have compared lung delivery of ICSs via a nebuliser with a DPI or pMDI plus

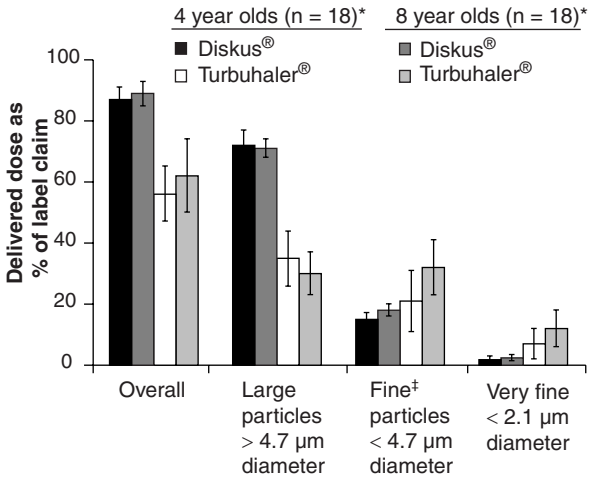

Figure 4. Fine and very fine particle fractions according to age in children who received inhaled corticosteroids via the Turbuhaler® or Diskus® device. Data from Bisgaard *et al.* (1998) [55].
*All children used both devices. ‡Includes very fine particles.

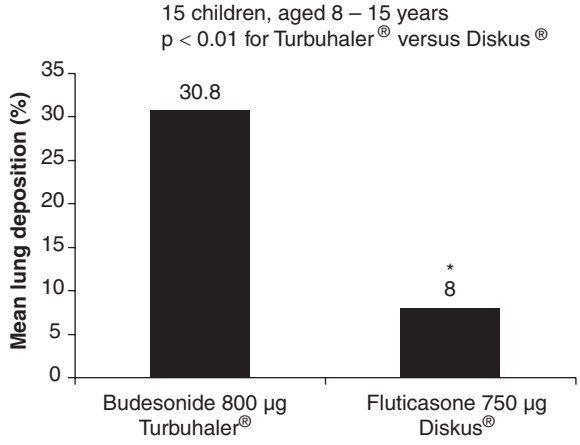

Figure 5. Absolute bioavailability of inhaled corticosteroids in children who used the Diskus® or Turbuhaler®.
*Coefficient of variation for budesonide Turbuhaler versus fluticasone Diskus, 24.2 versus 61.2%. Data from Agertoft and Pedersen 2003 [62].

spacer in children with asthma. However, *in vivo* comparative studies have described paediatric lung deposition of SABAs. One such trial was a filter study that compared the aerosol delivery of salbutamol from the PARI Baby nebuliser with that from a pMDI with a small volume spacer (Babyhaler or NebuChamber) in wheezy infants 4 – 12 months of age [63]. Mean drug deposition on the filter was ~ 40% of the activated pMDI dose using either spacer compared with 25.3% of the nebulised dose. However, because the nebulised dose was greater than the actuated doses from the pMDI/spacers, the absolute dose from the nebuliser was greater (260.1 µg) than those of the pMDI/spacers (150.3 µg, Babyhaler; 153.8 µg, NebuChamber) [63].

Another study used radiolabelled salbutamol to compare the efficiency of aerosol delivery from the nebuliser and a pMDI with chamber in 17 children (2 – 9 years of age) with asthma [64]. Both younger (2 – 4 years) and older (5 – 9 years) children had significantly higher absolute values of salbutamol lung deposition from the nebuliser compared with the pMDI. However, the devices were equally efficient in the delivery of salbutamol to the lungs [64]. No differences were observed in the percentage of lung deposition from either device within each age group; however, the percentages of lung deposition from the nebuliser and pMDI were greater in the older children than in the younger children [64-66].

7.1 Clinical efficacy

The ACCP/ACAAI guidelines reviewed outcomes from four paediatric studies that compared devices containing SABAs [12]. Two studies compared the delivery of terbutaline via pMDI and DPI (Turbuhaler), one study evaluated fenoterol delivery by pMDI and DPI, and the last study, which included children and adults, analysed the administration of budesonide from a pMDI with or without a spacer [67-70]. According to that meta-analysis, data from the four paediatric studies, individually or combined, indicated that there was no difference in efficacy (e.g., FEV_1) between the pMDI and DPI devices (Figure 6) [12]. Similarly, an earlier study that reviewed comparative data on asthma delivery devices in children reported that no studies reported any significant difference between the devices. A meta-analysis could not be performed because of the lack of extractable data and the differences in devices and ages [71].

Other studies have compared the efficacy of budesonide Turbuhaler versus fluticasone Diskhaler in children aged 5 – 16 years [72], and budesonide Turbuhaler versus pMDI with Nebuhaler in children aged 4 – 15 years [73]. No differences in efficacy were observed between the budesonide Turbuhaler and fluticasone Diskus in the DPI study [70]. The DPI versus pMDI study demonstrated that the delivery of budesonide via Turbuhaler was associated with a lower requirement for rescue medication compared with delivery via pMDI/spacer (95% confidence interval 0.34 – 1.96) [73].

There are no known studies that have compared the use of ICS delivered by DPI or MDI devices with that of a nebuliser. Noncomparative studies in children have demonstrated the safety and efficacy of ICS delivered via nebuliser, MDI or DPI for the treatment of persistent asthma. The efficacy of ICS, particularly budesonide inhalation suspension, delivered via nebuliser is well established for young children [74-78]. Data describing the efficacy of ICS delivered via MDI devices are available in older children [79]; however, data in preschool-aged children are limited [80,81]. Similarly, efficacy

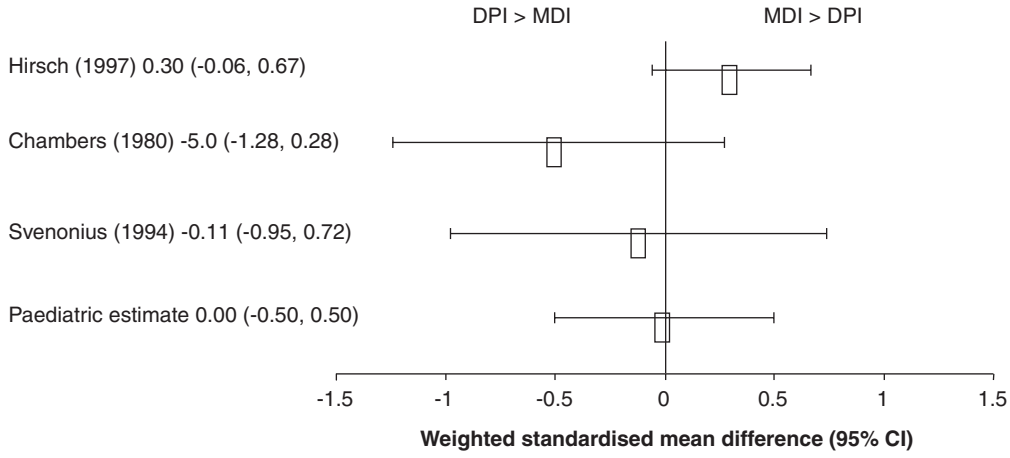

Figure 6. Meta-analyses results comparing the clinical responses to short-acting β_2-adrenergic agonists delivered via MDI versus DPI to paediatric patients. Weighted standardised mean difference for combined end point (forced expiratory volume in 1 s, peak expiratory flow rate, or specific airways conductance) in out-patient β_2-agonist trials comparing MDI versus DPI [12,67-69]. Reproduced with permission from DOLOVICH MB, AHRENS RC, HESS DR *et al.*: Device selection and outcomes of aerosol therapy: evidence-based guidelines. *Chest* (2005) **127**:335-371 [12].
CI: Confidence interval; DPI: Dry powder inhaler; MDI: Metered dose inhaler.

data for DPIs are primarily available in children older than 4 years [82-89].

8. Expert opinion

In respiratory disease, it is critical for physicians to understand the delivery of aerosol medications, the preferred administration route for both reliever and controller medications used in the treatment of asthma [30]. Choice of a delivery method is just as important as the choice of medication itself [90]. For example, the use of a lower potency ICS may result in asthma control comparable with that of a higher potency ICS if the former is administered in a more efficient device (e.g., hydrofluoroalkane-beclomethasone dipropionate pMDI) [91,92]. Multiple factors influence the selection of the most appropriate aerosol delivery device for a particular patient. Because of the large number of aerosol delivery devices on the market, it is important to be aware of their specifications and limitations, their local availability and coverage on formulary. Furthermore, physicians require information and guidance concerning the benefits, risks and proper use of delivery device alternatives [12]. Physicians should remain current with the clinical application of available therapeutic options and receive periodic reinforcement in the correct use of various inhaler devices [46].

Clinicians should understand the aerosol characteristics that are associated with a particular drug and device. For example, are the majority of particles delivered within the respirable range? Do clinical studies suggest that young children receive a consistent amount of drug from the chosen device? Patient breathing patterns also must be considered. Inspiration through the nose may result in little or no delivery from MDIs and DPIs, neglecting to hold the breath results in reduced deposition from MDIs, and slow inspiration or breathing into the device reduces delivery from DPIs [93].

Clinicians must consider the aforementioned factors to ascertain whether the chosen device will provide appropriate lung deposition with a predictable delivery. Although information is available for most of the delivery devices of large pharmaceutical companies, comparative studies and other information are lacking for many generic delivery devices. ICS devices that have been insufficiently characterised should not be used for maintenance therapy [90]. Similarly, products and formulations that have not been subjected to the rigorous testing required by regulatory authorities should be avoided (e.g., compounded formulations of nebulised medications).

It is essential that the prescribing clinician is able to estimate the abilities of the children and their parents because the effective delivery of aerosol medications in children is contingent on an appropriate delivery device–patient match [90]. Several factors can guide clinicians on choosing the optimal delivery device for a particular child. The clinician must have a thorough understanding of the pathophysiology and severity of disease and must consider the age and skill level of the patient when considering the complexity of the device. Patient age is a critical variable to consider when choosing both the asthma medication and its method of administration. Even if an age-appropriate device is selected, ongoing education and

instruction are required to ascertain that the device is used correctly. Even with an understanding and knowledge of how to use the device optimally, ineffective use may unintentionally occur [9]. Third-party payors also influence device selection and may result in the patient not receiving the optimal delivery system. Finally, acceptance of a particular therapy is critical to ensuring therapeutic success [9]. The ideal device is one the patient or caregiver can use correctly and facilitates adherence to prescribed asthma therapy.

Disclaimer

William E Berger has received grant, research and editorial support from Altana, AstraZeneca LP, Aventis, Genentech, GlaxoSmithKline, MedPointe, Merck, Novartis, Pfizer and Schering. He is on the speakers bureau for AstraZeneca LP, and acknowledges the support of AstraZeneca LP and the editorial assistance of Marissa Buttaro with Thomson Scientific Connexions in the preparation of this manuscript.

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