UPDATE ARTICLE
ARTICOLO DI AGGIORNAMENTO

Aerosol therapy

Aerosol terapia

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Summary

Aerosol therapy in children has increased considerably in both sophistication and scope, and the advantages of this route for the delivery of a variety of drugs have become well recognized.
This review describes the physical properties of aerosols that influence lung deposition, followed by a review of the most common methods of aerosol generation. The last part of the paper is devoted to recent developments in our understanding of aerosol delivery to infants and young children, a relatively neglected and under appreciated area in aerosol therapy.

Riassunto

L'aerosol terapia nei bambini è migliorata significativamente ed è divenuta più efficace; i vantaggi di somministrazione di diversi farmaci per questa via sono ormai riconosciuti. Questo articolo descrive le caratteristiche fisiche degli aerosol che influenzano la deposizione nei polmoni di tali farmaci; segue una revisione dei metodi più comuni di generazione degli aerosol. L'ultima parte dell'articolo è dedicata ai recenti sviluppi nelle conoscenze relative alla somministrazione a neonati e bambini piccoli, un aspetto relativamente trascurato e sottostimato.

Key words

Aerosol • Inhaled therapy • Children • Infants • Nebulizers

Parole chiave

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Introduction

The administration of drugs directly into the respiratory tract for the treatment of lung disease in children seems logical means, since in theory, the drug will have its maximal effect on the diseased lung, and side effects on other organs would be minimized. The value of aerosol therapy was recognized by ancient civilizations in India, China, and the Middle East, as well as by Hippocrates and Galen [1].
During the past half century, inhalation treatment has increased considerably in both sophistication and scope, and the advantages of this route for the delivery of a variety of drugs have become well recognized. The drugs usually begin to act very rapidly, and as a smaller dose can be used than with oral or intravenous delivery, there is generally a reduction in the incidence of systemic side effects and cost.
For an aerosol device to efficiently deliver medication to the lower respiratory tract it must be able to generate a cloud of medication particles with the majority of these particles being sufficiently small for efficient inhalation and deposition in the airways [2].
This review will describe the physical properties of aerosols that influence lung deposition, followed by a review of the most common methods of aerosol generation. The last part of the paper will be devoted to recent developments in our understanding of aerosol delivery to infants and young children, a relatively neglected and under appreciated area in aerosol therapy.

Aerosol size and deposition

An aerosol is defined as a suspension of liquid droplets or solid particles in a gaseous medium. The particles remain suspended because of a low terminal settling velocity. The terminal settling velocity of a particle is the velocity that the particle will fall in air due to gravity. This velocity is related to the diameter and density of the particle. Most therapeutic aerosols are heterodisperse; that is, the aerosol cloud contains a range of particles that vary considerably in size. Heterodisperse aerosols of different densities and irregular shapes can be described in terms of a single parameter, the mass median aerodynamic diameter (MMAD), which is the function of the sedimentation velocities and impaction characteristics of the particles within the aerosol [3 4].

For a uniform and spherical particle this is defined as the particle diameter multiplied by the square root of the particle density which, for water, would be 1; the MMAD of all other particles can be related to this. Because particles are non-uniform in terms of density and shape, particles are usually sized by their settling behavior on a series of baffles in a cascade impactor. This yields information not only on the MMAD but also on the particle size distribution or geometric standard deviation (GSD). By definition, a GSD of < 1.22 defines a monodisperse aerosol. Nearly all therapeutic aerosols are heterodisperse but the smaller the GSD the greater the proportion of particles will be around the MMAD. In general the so-called respirable fraction of a therapeutic aerosol consists in particles with a volume between 0.5 and 5 μm MMAD. Unfortunately, this term has caused some confusion since it is often assumed that the respirable fraction is actually deposited in the lower respiratory tract. In fact, it is particles in this size range that simply have the highest probability of being deposited in the lower respiratory tract. Thus the term "Respirable Fraction" is being replaced by a statement of the actual aerodynamic size as expressed by the MMAD and GSD of the heterodisperse aerosol. Particles larger than 5 μm have a greater probability of impacting in the oral pharynx which results in their being swallowed, with systemic effects and loss of medication due to degredation by gastric acid and enzymes. Oral pharyngeal deposition may cause thrush or laryngeal dysfunction with inhaled corticosteroids (ICS). Very large particles will probably deposit in the aerosol generation and delivery system whereas extremely fine particles are less likely to sediment in the airway and are thus exhaled.

The three major mechanisms of aerosol deposition are inertial impaction, gravitational sedimentation, and diffusion [5 6]. Each mechanism has an at least theoretical impact on aerosol delivery to infants and small children. Inertial impaction is the primary mechanism for deposition of particles > 3 μm. Smaller diameters of upper and lower airways in infants and children result in a greater percentage of particles in this range impacting in the structures of the upper airway. In addition, preferential nose breathing in young children further filters aerosol from inspired gas, reducing the mass of drug available for pulmonary deposition [7]. Inertial impaction is highly flow dependent, so that during high inspiratory flow there is a greater probability of smaller particles impacting in the upper respiratory tract (i.e. above the vocal cords). In contrast, low inspiratory flow or low density particles are more likely to by-pass the upper airways and be deposited by sedimentation in the lower respiratory tract.

Gravitational sedimentation describes the effect of gravity on particles that have not been deposited by inertial forces. This is the primary mechanism of deposition for particles with MMAD < 3 μm, but also applies to larger particles under low flow conditions or with a low density. The longer particles reside in the lung, the greater their deposition. It is for this reason that breath holding for 5-10 seconds is recommended after inhalation of an aerosol to maximize sedimentation time and increase deposition in the lung periphery. The low tidal volume, relatively small vital capacity (VC) and functional residual capacity (FRC) and short respiratory cycle of infants [8] result in a shorter residence time for small particles in the lungs, and thus decreased pulmonary deposition.

Diffusion primarily affects particles so small (MMAD < 0.1 um) that Brownian motion has a greater influence on particle deposition than gravity. Random Brownian motion results in collisions with both airway structures and other particles, the latter resulting in particle coalescence. Particles tend to coalesce, or be attracted by the mass of other objects, due to gravitational forces, when they are within a distance of less than 25 times their diameter. At present this mechanism has no clinical relevance since it is not applied in any aerosol therapy.

Aerosol delivery systems – overview

Therapeutic aerosols may be generated and delivered by small volume liquid nebulizers (SVN), pressurized metered dose inhalers (pMDI), or by dry powder inhalers (DPI). SVNs and pMDIs are considered "active" devices, as they generate the aerosol particles independent of the patient's effort, in a deaggregated form suitable for inhalation. DPIs can be either "active" or "passive" devices. Passive devices require vigorous suction by the patient to deaggregate the powder while simultaneously inhaling the medication (Tab. I).

Small Volume Nebulizers (SVNs)

Jet Nebulizers

The majority of currently used commercial nebulizers were developed from squeeze bulb devices. They utilize compressed gas to generate liquid aerosol droplets by means of a Venturi that operates on the Bernoulli principle – namely acceleration of gas through a small orifice directed across a liquid-filled capillary tube [9]. This causes a fall in pressure at the capillary orifice that

Tab. I. Aerosol generation and delivery devices.

Small Volume Liquid Nebulizers (SVN)	Jet	
	Ultrasonic	
	Atomizers*	– Multidose Drug Reservoir with microscreen; piston driven compressed air (e.g. Respimat, Boehringer Ingelheim Pharma, Ingelheim am Rhein, Germany);
		– Unit dose blister (e.g. AeRx, Aradigm corp, Hayward CA USA)
Metered Dose Inhalers (pMDI)	Press & breathe	
	Breath activated (e.g. Autohaler, 3M, St Paul MN, Easy Breathe, Ivax, Miami, USA)	
pMDI with Accessory Devices	Spacers- simple extension tubes	
	Valved holding chambers (VHC) with mouthpiece or masks.	
Dry Powder Inhalers (DPI)	a) Passive (e.g. Rotahaler, Diskhaler and Diskus, Glaxo Wellcome Ware UK, Clickhaler ML Labs, St Albans UK, FO2 Boehringer Ingelheim, Ingelheim Germany, Turbuhaler, Astra Zeneca, Lund Sweden)	
	b) Active*:	Battery powered turbine (e.g. Spiros, Dura Parmaceuticals, Berkeley CA), Compressed air driven (e.g. Powder Delivery System (PDS), Nektar Therapeutics, San Carlos CA)
	Mechanical (spring driven) scraper (Maghaler, Frankfurt, Germany)	
	Vacuum (mechanical suction) - activated (e.g. ML Labs, St. Albans UK)	

* All still experimental.

causes the drug solution to be forced through the capillary from a reservoir by atmospheric pressure. The liquid is thus turned into an heterodisperse aerosol containing a range of sizes with a geometric standard deviation (GSD) greater than 1.22. The larger droplets are removed by baffles, while particles below 10 um and down to approximately 0.5 um mass median aerodynamic diameter (MMAD) are inhaled into the lower respiratory tract (LRT) with increasing probability as their aerodynamic diameter decreases. LRT delivery efficiency peaks at about 80-90% for particles of approximately 1-2 um delivered to the mouth in normal adults inhaling at ~ 0.5 L/sec from functional residual capacity to total lung capacity [10]. The major problem with jet nebulization is that the primary droplets are relatively coarse. In order to filter out the larger droplets (over 5 um) and limit as much as possible the output to the lung targetable dose (MMAD < ~ 3 um), inertial filtration is used. Nebulizers which deliver fine aerosols do so by baffling out and recirculating coarse droplets. This produces smaller particles better suited for targeting to the LRT and reduces oropharyngeal deposition. The disadvantage is very inefficient aerosol delivery resulting in long nebulization times that may lead to reduced compliance among children and adolescents. Overall LRT deposition is usually no more than 8-10%, due mainly to the nebulizer "dead volume" (residual drug in the nebulizer reservoir and on the walls) and aerosol losses from the JN to the environment during the exhalation phase of tidal breathing with continuously operating devices and contained in the exhalation with aerosols below about 1.5 um MMAD, e.g. 18% with QVAR, (3M, St Paul, MN), (MMAD 1.1 um, GSD 2.5), even with breatholding. This effect is likely to be even greater during tidal breathing of very small aerosols. Increasing the fill volume intensifies the overall drug delivery efficiency (DDE) to the mouth but prolongs the nebulization time. Using undiluted, very concentrated drug solutions may reduce the nebulization time for a given dose, if the resulting solution is not very viscous, but is wasteful of medication. However, this may not be an important issue with inexpensive agents. Advantages of SVNs include relative ease of use (patients can inhale from nebulizers by tidal breathing without the need to coordinate inspiration and aerosol delivery), and ability to aerosolize large volumes (up to 15-20 mL/hour with large-volume nebulizers) and for providing medications (e.g. large peptides) that are not formulated for delivery by pMDIs or DPIs.

The disadvantages of SVNs include: cost – the compressors required to drive the nebulizers are relatively expensive ($ 120-150) although less expensive, but perhaps less robust compressors are now available; longer administration time – an average treatment lasts 10-15 minutes; discomfort – younger children may not tolerate the tightly fitting mask and the compressor noise for more than a few seconds and may cry, thus getting little, if any medication [11]; inconvenience – compressor driven nebulization systems are bulky, not readily portable, need a power source and require frequent cleaning to prevent contamination [12]. Another disadvantage of nebulizers is their lack of standardization that has led to considerable (as much as 10-20 fold) inter- and intramodel variability, the latter suggesting poor quality control [13 14]. Having recognized that a serious problem exists in this regard, European and North American committees have been formed to develop standards for nebulizers.

Ultrasonic Nebulizers

Ultrasonic nebulizers (USN) produce aerosol particles by means of high frequency vibration of a vibrating

piezoelectric crystal (VPC) [9]. The advantage of USNs is that they may deliver a large volume of aerosol over a reasonably short period of time. When choosing USNs, it is important to ensure that they are sufficiently powered to produce therapeutic aerosols of particle size appropriate for efficient airway and lung deposition. Some of the earlier under-powered USNs generated inappropriately large particles most of which were deposited in the oropharynx (e.g. Siemens-Bosch, Munich Germany). The LRT deposition efficiency of such devices rarely exceeds 3%. Durability of USNs has been an ongoing problem since saline tends to crystallize around the circuit of the USN causing malfunction. As the USN empties, there is considerable stress on the crystal, which may cause it to crack and fail. Current designs use a number of electronic tricks such as load sensing and automatic frequency matching to control crystal temperature and increase reliability. Examples of new development include VPC USN with fixed microscreen (Omron, Osaka, Japan), or VPC USN with vibrating screen (Pari, Munich, Germany).
Other disadvantages of USN devices is their tendency to denature peptide medications due to relatively high temperatures, their inefficiency for nebulizing drug suspensions [15], their generally larger droplet size, and their high cost.

Small Volume Nebulizers: lower respiratory tract drug delivery efficiency (LDE)

A major problem with nebulizers is that they have a large internal "dead volume" and up to 50% of a 3 ml fill usually remains trapped inside the nebulizer body on the walls and baffles and in the tubing [16]. Overall LDE varies greatly between 5 and 15% (rarely > 10%) and nebulization time varies between ~ 5 and 20 minutes depending on volume and viscosity of the drug solution.
Most nebulizers deliver aerosol continuously whereas patients only inhale for approximately 30-50% of the respiratory cycle. Thus, the dose available to be inhaled into the LRT is half or less of that delivered to the mouth. In general only about 10% or less of the drug dose placed in the nebulizer actually deposits within the lower respiratory tract even with optimal inhalation technique, although as much as 15% LRT deposition has been achieved if the carrier air is dry.
There is room for improvement in nebulizer design and standardization. Some newer nebulizers have interrupters or inspiratory control valves that allow synchronization of aerosol delivery and inspiration. Others have holding chambers or "reservoirs" that fill during exhalation and are emptied on inspiration. Newer designs incorporate an extra vent into the nebulizer in such a way that the negative pressure generated by the expansion of compressed air at the Venturi sucks air into the chamber via the vent as well as fluid for atomization from the feeding capillary tubes. This “open vent" design results in greater airflow through the chamber, thus delivering smaller particles and shortening nebulization time as a result of increased evaporation. Other designs have used electronic (e.g., Optineb, Air Liquide, Paris France) or manual interrupters. The latter require coordination by the patient and, due to the time required to achieve maximum flow, will initially generate larger particles, reducing LDE while at the same time, prolonging somewhat the duration of administration.
The recent generation of nebulizers was designed to combine the convenience of continuous operation and the efficiency of intermittent nebulization. One design (Pari LC Plus, Pari, Germany) nebulizes continuously, but a valve on top of the device opens only during inspiration, allowing extra air to be drawn through the nebulizer. As with the open vent nebulizers, it is claimed that this air will draw a greater number of lung targetable particles into the inspired air stream. During exhalation the inspiratory valve closes, decreasing the flow of air through the chamber to that from the compressor only. This limits losses of aerosol during exhalation to that from a conventional jet nebulizer. Likewise, the Ventstream (Inspired Medical Products, Pagham, West Sussex, UK) has a valve which opens only during inspiration, allowing air to be drawn through the nebulizer to increase drug output. On exhalation this valve closes as exhaled air passes out of the device through a separate expiratory pathway. These "breath assisted, open vent" nebulizers increase the LDE and reduce wastage [17]. Another recent development by Trudell Medical International (London, ON, Canada) is an inexpensive, disposable jet nebulizer that mechanically generates aerosol on demand only [18]. This device uses a spring-loaded diaphragm to separate the drug solution-containing feed tube from the air jet during exhalation. At the onset of inhalation the liquid feed tube and air jet are aligned by the negative pressure, and aerosol generation is initiated.

Pressurized Metered Dose Inhalers (pMDIs)

pMDIs are small spray cans that have been the standard for about half a century for targeting most aerosolized drugs to the pulmonary airways. pMDIs have traditionally used chloro-fluorocarbon (CFC), 12 and 114 with high vapor pressure at room temperature as the power source and CFC 11 which is liquid at room temperature as the suspending liquid, or solvent for the drug. pMDIs are by far the most popular aerosol generators and account for about 70% of the 500,000,000 aerosol therapy devices sold annually worldwide. They accurately and reproducibly delivered a metered dose of CFC-pressurized drug suspension or solution (except for the first puff after the MDI has not been discharged for several hours). However, CFCs are rapidly being replaced by newer more ozone friendly propellants such as hydro-fluoro alkane (HFA) 134a or 227. The HFA 134a beclomethasone formulation (QVAR) developed by 3M, provides relatively small uniform droplet aerosols [MMAD of ~ 1.1 um and gsd ~ 2] with LDE of 50-60%. This superfine solution aerosol more effi-

ciently deposits not only in large but also in small airways and alveoli even in the presence of airflow obstruction, since particles < 1.0 um behave increasingly like a gas as their MMAD decreases. On a dose per dose basis this superfine aerosol is more than twice as effective, and has a similar safety profile to the CFC formulation, a drug suspension with MMAD ~4 um and LDE about 10% [19]. With the QVAR formulation, only about 30% of the drug losses in the oropharynx are due to the ballistic component, and about 20% of the drug is exhaled, even after a 10 second breath hold. With the previous generation of CFC-formulated MDIs these values were 70-80% in the oropharynx and < 1% exhaled.

pMDIs consists of 3 major components: a reservoir containing drug particles in suspension or drug solution in pressure-liquefied inert gas propellant; a metering valve, which when depressed reliably delivers a fairly precise quantity of the reservoir contents; and a spray actuator, which together with the stem of the metering valve comprises a twin orifice expansion chamber and spray nozzle that directs the aerosol towards the mouthpiece of the pMDI.

The main advantages of pMDIs are their small size, multidose convenience, versatility (with appropriate attachments), higher LDE, dose reproducibility from puff to puff, freedom from bacterial contamination, and a light, self contained power source. Additional important benefits include ergonomic similarity from manufacturer to manufacturer, multiple dose capability, rational drug combinations within the same canister (e.g. sympathomimetic with parasympatholytic or with corticosteroids) and lower cost per dose. Unlike most passive DPIs, whether reservoir type (e.g. Turbuhaler, Astra-Zeneca, NJ, USA) or unit dose blister, (e.g. Diskus, GSK, Ware, UK) pMDIs are much less affected by high humidity, although humidity may also be a problem with these devices.

The main disadvantages of pMDI, especially in young children, is that, when used alone, they may be difficult to administer since they require considerable hand-breath coordination by the patient or caregivers to achieve optimal benefit. Breath-activated pMDIs that provide medication only on inspiration are available with some drug formulations and may prove useful in older children (> 6 years) as well as in adults with poor coordination who can reliably achieve the inspiratory flow of 25-30 L/min necessary to activate them. Another disadvantage is release of aerosol at high velocity (~ 100 kph). This ballistic effect, more marked with the larger, high inertia aerosol droplets, causes deposition of approximately 65% of the medication from CFC-driven devices (~ 30% with HFA-QVAR) in the upper respiratory tract (mouth, oropharynx and larynx) (URT). This URT dose contributes considerably to increased systemic absorption and side effects and also to local side effects (dysphonia, gagging or burning sensation, candidiasis, bad taste) in the oropharynx and larynx [20]. The low temperature of the CFCs or HFAs discharged from a pMDI frequently causes children to abruptly stop inhaling (cold freon effect). During the past decade, the possible contribution of CFCs to destruction of the stratospheric ozone layer became an increasing environmental concern and as a result of the Montreal protocol, an international agreement was reached to ban the manufacture and use of CFCs in developed countries, with a year to year exemption for any remaining essential medical purposes.

This will become absolute in the developed nations starting in 2005 and in third world by 2012. It was this that caused the chemical and pharmaceutical industries to develop innovative substitutes using HFA 134a (also used increasingly for refrigeration, foaming plastics etc.) and 227 instead of CFC12 and 114. Unfortunately, there is no ready substitute for CFC 11, which has made reformulation of pMDIs very challenging and has led most companies involved in treating asthma to aggressively develop and market DPIs.

pMDI Accessory Devices: Spacers and VHCs

During the past 20 years, these "low tech" and inexpensive pMDI add-on units have evolved into highly sophisticated patient and task-oriented devices that have had a major impact on aerosol delivery for children. The addition of valved holding chambers to pMDIs reduces problems of hand-breath coordination, by dissociating aerosol discharge and inhalation. They also considerably decrease (by about 90%) ballistic drug deposition in the oropharynx and reduce total body dose by 75%, improve the LDE of small aerosol particles by 30-50%, increase the therapeutic ratio, and facilitate patient and task-specific aerosol delivery [21].

MDI accessory devices began as simple tubes or containers (e.g. coffee cups, toilet rolls, modified 1-1.5 L plastic flasks), which were appropriately named spacers. The main benefit of spacers, is to extend the distance between the actuator and the mouth thus allowing the larger aerosol particles that have little or no therapeutic benefit to decelerate and deposit in the spacer thus reducing ballistic and inertial impaction of particles in the URT. The spacer may, depending on its volume and configuration, allow larger droplets to evaporate before reaching the humid environment of the oropharynx, thus increasing the dose of LRT-targetable medication. This results in a decrease in systemic absorption and adverse effects. The main rationale behind the development of pMDI accessory devices was to provide a reservoir of aerosol, from which the patient could breathe, thus removing the need to coordinate the actuation of the inhaler with inspiration. While spacers still require hand-breath coordination, the development of relatively simple and practical VHCs almost completely overcame this problem. Furthermore, VHCs with masks enabled the use of pMDIs instead of nebulizers in relatively uncooperative, tidal breathing patients such as the confused elderly and adults or children with severe shortness of breath (e.g. during acute severe asthma). The addition of a face mask to the VHC also allowed pMDIs to be used successfully in infants and children from birth to 3-4 years of age who

are too young to breath through a mouth piece. Using a VHC also allows more CFC or HFA to evaporate and traps excipients such as oleic acid. This results in a greater mass (by up to 40%) of smaller drug particles [22], which improves not only drug penetration, but also the dose delivered to more peripheral airways and clinical outcomes [23].

Some larger MDI accessory devices (up to 750 ml) are relatively bulky and children will usually be reluctant to use them in school. Large VHCs provide little greater output in the particle size range under 2-3 um than 150 ml devices [22], nor have they been shown to produce additional clinically relevant benefit [23 24]. Indeed, for treating infants with low tidal volumes, chambers of approximately 150 ml are superior in LDE to those over 200 ml [25-27]. Several other factors such as mask fit, dead space and electro-static charge [28-32] are also important in holding chamber design.

Dry Powder Inhalers (DPIs)

Currently these are all "passive" devices requiring vigorous rapid inhalation, ideally from FRC, to release and deaggregate the drug. Active (powered) and highly efficient DPIs now undergoing clinical trials will probably be available within 2 years, although it is unlikely that their greater cost will warrant their substitution for current devices unless the medication itself is very expensive.

In principle, the drug formulated as a dry powder is dispersed in the inspiratory air stream when the child inhales rapidly and vigorously through the DPI. Since the drug is only aerosolized and delivered during inspiration, "hand/lung" coordination is ensured. DPIs have therefore found considerable popularity and widespread acceptance and now have about 70% of the market. However, with most of these DPIs the high initial airflow required to disperse the drug powder creates a ballistic effect and upper respiratory tract (URT) deposition quantitatively similar to pMDIs. DPIs are small unobtrusive and thought to be relatively easy to teach although, in practice, they may be used suboptimally by patients about as commonly as pMDIs [33-35]. The Bricanyl (terbutaline) and Pulmicort (budesonide) Turbuhalers contain only pure drug without the lactose carrier common to most other formulations. Some Turbuhalers have recently been formulated with a lactose carrier (e.g. Inspiryl) to increase the total mass metered. This should improve the reliability of dosing compared to pure drug powder devices which have had considerable difficulty meeting FDA requirements for dose and fine particle fraction reproducibility between and within batches, mainly due to the minute amounts of drug being metered (e.g. 12 ug formoterol). Whereas first generation DPIs were single dose inhalers (Rotahaler Glaxo Wellcome UK, FO2 Boehringer Ingelheim Germany and Spinhaler Fisons, Loughborough UK), in recent years multi-dose devices [e.g. Turbuhaler Astra Zeneca, Lund Sweden, Diskhaler and Diskus (Glaxo Wellcome, Ware UK), Clickhaler (ML Labs, St Albans UK) or Easyhaler (Orion, Helsinki Finland)] have become available. With most passive DPIs, an inspiratory airflow of 30-60 l/min must be generated rapidly to optimally disperse the powder into small particles (at least 60 l/min in the case of Turbuhaler which is particularly flow sensitive). Small children under 6 years of age and older patients with severe air flow obstruction may not be able to generate sufficient inspiratory flow to efficiently disperse the powder. Other disadvantages include powder clumping particularly under conditions of high humidity and relatively low flow, especially with devices with a drug reservoir exposed to the environment, and with hygroscopic drugs (e.g. Bricanyl Turbuhaler) [36 37]. There is also the limitation of airway irritation and coughing (particularly with devices that use large doses of lactose as a dispersant).

This results in another potential problem that arises from the ergonomic variety of DPIs from various manufacturers as well as the marked differences in inhalation technique between passive DPIs and pressurized pMDIs that will doubtlessly confuse many patients who may, for example, use the Diskus for control of asthma but carry an albuterol MDI for use as needed. The slow inhalation taught for optimal use of the MDI and the diametrically opposed technique of rapid inhalation with the DPI tends to confuse patients and thus may adversely impact compliance and therapeutic outcome. The cost per dose with DPIs tends to be higher than pMDIs as well.

The main advantage of DPIs is that they are inherently breath actuated since they only deliver drug when the patient inhales. This paradoxically, is also a potential disadvantage. The de-aggregation and LDE is critically dependent on the patient's ability to generate a sufficiently high flow within 100-200 milliseconds [38]. This is a particular problem with small children or patients in severe acute respiratory distress, particularly with high resistance devices such as the FO2 and Turbuhaler.

With active or powered DPIs, the energy required for powder de-aggregation is provided by compressed air, a battery driven turbine, or vacuum [39]. The aerosol can then be inhaled at a low flow by the patient. These devices are still experimental but hold considerable promise since they may be able to replace SVNs for providing the relatively high payloads of mucoactive medications, antibiotics and drugs for systemic therapy such as insulin or vaccines, as appropriate formulations become available. With DPIs, therapy could be accomplished in 1-2 minutes in contrast to the 10-20 minutes required for SVNs. Furthermore, the LDE is likely to be 3-4 fold greater thus reducing the 75% or more of the medication wastage resulting from the nebulizer and tubing dead volume and continuous operation.

Infants and preschool children

Young children, particularly infants, are a special subpopulation with regard to aerosol therapy. There are

various anatomical, physiological and emotional factors unique to infants that present significant difficulties and challenges for aerosol delivery. Of these, we believe that the single most important factor to consider in practice is the compliance of infants during aerosol administration. In this regard we will address two major practical issues. Application of the face mask and crying that is often associated with it.

Face mask

It is not until two and a half to three years of age that a child will develop sufficient understanding to use a mouth-piece. Consequently, a face mask must be used as the interface between the aerosol generator and the patient.

Clearly, it is the face mask that is the major factor in infant aerosol delivery and this has been fully appreciated only fairly recently since in several studies it is evident that comfortable, yet tightly fitting, masks are a prerequisite to efficient aerosol delivery in tidal-breathing infants.

Several recent studies emphasized the importance of a tight seal between the face and the mask rim. Everard pointed out, more than a decade ago, that even a 1 cm gap between the mask and the face reduces the dose delivered by 50% [40]. We and others have recently compared the effectiveness of the seal of various face masks and showed the effect of the seal on aerosol delivery [29 41]. Any gap between the mask and the face will lead to greatly reduced efficiency. The potential impact of a poor seal appears to be greater for MDIs with valved holding chambers since no drug is delivered unless the infant is inhaling from the device. There is also a marked effect on the dose inhaled from jet nebulizers. Breaking the seal results in entrainment of fresh air. As is frequently the case, facemasks available for children have frequently been merely smaller versions of those used for adults with little consideration given to the special needs of infants [42].

That the face-mask fit is important in day-to-day clinical practice, has also been demonstrated by Jenssen et al. who showed increased variability with the poorly-fitting mask supplied with the Nebuchamber VHC [43]. We recently improved the performance of the Nebuchamber by developing an improved mask with a much better seal, and this was shown to improve the delivery efficiency of therapeutic aerosols in young children by 30% [44]. It was used successfully in a study of infants and young children with acute asthma presenting to an emergency department [45]. A similar attempt to improve the face mask fit in clinical settings was reported by Esposito et al. [46] who attached another round facemask to the Nebuchamber.

Surprisingly, both in our study and that of Esposito et al., the dose variability was not improved with the improved mask, but instead increased with decreasing cooperation. This leads us to suggest that while the mask configuration is indeed an extremely important factor in determining the aerosol dose delivered, this is probably less important than the magnitude of the daily variation, which depends mainly on patient compliance and cooperation.

The interaction between crying and the mask to face seal is complex. It is likely that the tightness of the fit between the mask and the face of the child and the insistence and increasing frustration of parents is the cause for crying. Indeed it has been suggested that the commonest cause of a poor seal is crying and/or distress associated with the treatments [47]. Which is the cause or the effect? Ritson et al. suggested that the requirements for a seal in their patients induced distress and affected efficiency of aerosol delivery [48]. Similarly Margot has also demonstrated that crying occurs in a significant part of young patients receiving inhaled therapy [49]. So crying is very common and may be inevitable unless perhaps the child is well prepared by making a game out of fitting the mask, perhaps at a time when the child does not need to use it.

What are the Effects of Crying on Aerosol Delivery?

Crying was believed originally to have no detrimental effect or even to improve delivery due to the large breath that usually follows the end of the cry. In fact, crying is a very long exhalation followed by a very rapid and brief inhalation. During nebulizer treatment, the aerosolized drug is unavailable during exhalation and during a very fast inhalation inertia of the inhaled medication the aerosol will likely deposit in the oral pharynx rather than in the airway. As well, patient agitation makes it less likely that there will be a good seal with the face mask.

Only anecdotal information is available regarding the relationship between behavior of the infant during aerosol therapy and respiratory tract deposition. Tal et al. [50] reported that lung deposition during crying in two of their patients who inhaled MDI-generated salbutamol from a valved holding chamber (Aerochamber, Trudell Medical International, London, ON, Canada) with mask was only about 0.35%, in contrast to a mean of 2.5% when breathing quietly. Murakami et al. [51] also reported that lung deposition in crying infants using a nebulizer and mask was negligible (scintigraphic data was provided for only one patient). Wildhaber and collegues [52] recently described their experience with one crying child whose lung deposition was markedly reduced compared to his non-crying peers. Moreover, the gastrointestinal deposition in this patient was 50% higher than the rest of the group with a 7 fold increase in the ratio of gastrointestinal (from swallowed aerosol medication) to lung deposition. Illy et al. [53], using urinary excretion of the drug has also shown reduced lung deposition when crying.

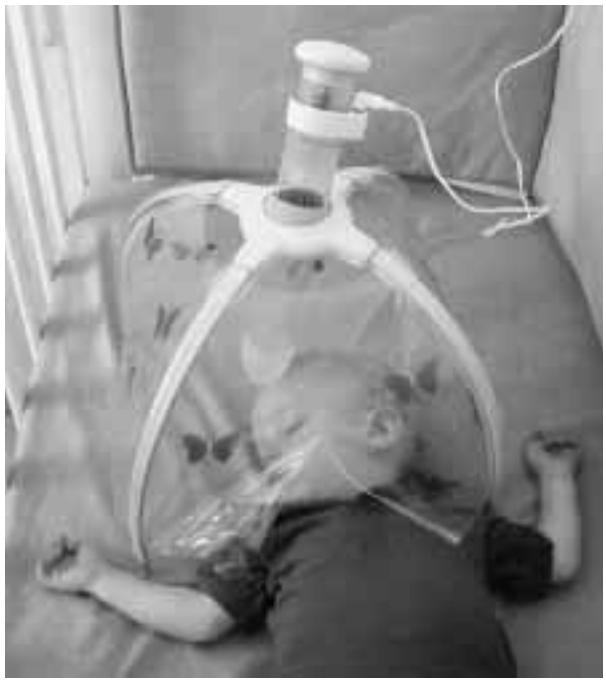
We recently showed [54], for the first time in an adequately-powered series of patients, that while there was no apparent relationship between infants' behavior and total lung deposition during aerosol therapy, there was a clear relationship between infants' behavior and deposition of aerosol in the URT that was subsequently swallowed and detected in the gastrointestinal tract.

The more distressed the infants were, the more aerosol was deposited extra-thoracically.
All these data help dispel the myth that aerosol delivery to the lungs of crying children is enhanced as a result of a deep inspiratory breath. This is probably related to the fact that crying or screaming infants adopt abnormal breathing patterns [55] such as a greatly prolonged expiration followed by short, high inspiratory flow velocity gasps leading to greater aerosol impaction in the throat [56] and frequent swallowing. While increased bronchodilator deposition in the URT and GIT may not be of great clinical significance in infants with asthma, this observation may be of greater concern during nebuliser treatments with corticosteroids [57] due to increased systemic absorption and a greater risk of adverse effects.
Thus, in contrast to previous assumptions, crying is now known to be detrimental and all efforts should be made to avoid it. Such efforts have been attempted by a recent in vitro study by Jenssen et al. [58], who showed that aerosol administration to sleeping children greatly improved aerosol delivery.

Compliance – dissatisfaction

It is a common complaint of parents of infants that it may be very difficult to keep a mask snugly fitted to the infant's face for more than a few seconds. Persisting with a screaming infant as parents may do, is not a good solution. Similarly, excessive pressure on the mask might encourage crying, hence a happy medium must be found.
The length of treatment with nebulizers, from 5 to 15 minutes, may be much more than awake infants will tolerate.
In despair, many parents resort to other alternatives thus aiming to avoid struggling with their baby during aerosol therapy. This has led to the common practice of blow by aerosol delivery using mask or tubing held near the child's face. The amount of drug delivered to babies using blow by is neglible [40] and this practice should be abandoned. A recent in-vitro study confirmed its inefficiency [59].
There is clearly a need to develop more acceptable and patient friendly interfaces for improving aerosol delivery to infants [2 46].
We have shown much greater delivery with a hood that significantly reduced crying in infants. So far a couple of studies have suggested a great potential for this mode of aerosol delivery to infants. A study carried out in the Pediatric Department, Sieff Hospital, Safed, Israel compared the lung deposition efficiency of nebulized aerosol delivered by face mask or via a prototype hood. 99m Tc albuterol solution was administered at random by nebulizer plus mask or hood to 14 wheezy infants (mean age 8 ± 5 mos). The dose and distribution of albuterol were evaluated using gamma scintigraphy. Clinical response, tolerability by the infants and parent preference were also compared.
Mean total lung deposition was 2.6% with the hood and 2.4% with the mask (p = ns). Variability with the mask was greater than with the hood (CoV = 54% *vs* 39%). Both treatments provided similar clinical benefit and side effects as reflected in improved oxygen saturation, reduced respiratory frequency and increased heart rate. Infants accepted the hood better than the mask and there was a positive correlation between poor acceptance and upper airways and stomach deposition for both treatment modalities. Parents preferred the hood treatments [54].
Because nothing comes into contact with the infant's face, this mode of administration is less likely to cause anxiety in infants and therefore there is less likelihood of crying. Not surprisingly, the hood is preferred by a significant majority of infant caregivers.
Another recent in-vitro study that compared delivered dose achieved with various nebulizers and interfaces, found that the best combination was the hood coupled with an Aeroneb Go (Aerogen Corporation, Mountain View, CA, USA) nebulizer, which uses an electronic micropump technology [59]. A commercially made hood (Child Hood, Baby's Breath, Yozmot Granot, Israel) specifically designed for infants is currently under development (Fig. 1).

Fig. 1. Child Hood device (Baby's Breath, Yozmot Granot, Israel) attached to Aeroneb (Aerogen, Mount view, CA, USA) nebulizer.



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