EXPERT REVIEWS

Aerosol therapy in infants and toddlers: past, present and future

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Infants and toddlers are a unique subpopulation with regard to aerosol therapy. There are various anatomical, physiological and emotional factors peculiar to this age group that present significant difficulties and challenges for aerosol delivery. Most studies on the factors determining lung deposition of therapeutic aerosols are based on data from adults or older children, which cannot simply be extrapolated directly to infants. The present review describes why infants/toddlers are very different with respect to two major issues – namely their anatomy/physiology and their behavior. We suggest possible solutions and future research directions aimed at improving clinical outcomes of aerosol therapy in this age group.

Keywords: aerosol • asthma • infant • inhaler • nebulizer

Infants and toddlers younger than 3 years of age are a unique subpopulation with regard to aerosol therapy. There are various anatomical, physiological and emotional factors peculiar to infants and toddlers that present significant difficulties and challenges for aerosol delivery. However, most devices used to administer aerosol medications to children are adapted from devices that were designed originally for adults [1]. Among the many devices used by children there are very few designed specifically for infants and toddlers.

We believe that, while there is a great need for infant-specific designs and technical improvements, the major impediment to efficient aerosol delivery to infants and to an understanding of the challenges posed by infants relates largely to an inadequate comprehension of the problem by most healthcare providers. This probably stems from insufficient knowledge and data regarding physiological and behavioral factors specific and quite unique to infants. Furthermore, many parents also are unaware that problems may arise when treating their infants with inhaled medications.

For example, if a baby is fighting the nebulizer facemask, mothers may substitute 'blow by' treatment in which the mask is removed from the tubing between the nebulizer outport and the open end of the tube is held close to the infant's nose or mouth. Alternatively, they may attempt to force the baby to accept the mask by holding them tightly, believing that aerosol administration to a crying infant is effective. When these parents report the rather poor response to therapy to their physician it is often assumed that aerosol delivery was adequate, resulting in an inappropriate increase in the aerosol dose or if the dose was previously maximal, the incorrect conclusion that the inhaled agent (usually inhaled corticosteroids [ICS]) was ineffective. In adults, there has been increasing evidence and thus clinical awareness of the importance of proper inhalation technique and compliance for the optimal management of reversible airflow obstruction with therapeutic aerosols, such as testing for sufficient inspiratory flow for dry-powder inhalers (DPIs), or regularly checking valved holding chamber (VHC) and metered-dose inhaler (MDI) techniques (e.g., all guidelines for adults recommend routine evaluation of correct inhaler technique at follow-up visits). By contrast, in pediatric guidelines it is unusual to find recommendations to check and correct inadequacies in aerosol delivery. This may be because there is relatively little evidence-based information or insufficient awareness among pediatricians (and family physicians) of similar problems in infants and toddlers – indeed, most pediatricians and family physicians do not routinely take the time to discuss adherence,

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particularly the mode of aerosol delivery, with infants' parents. Very often a prescription for a jet or other small-volume wet nebulizer is provided, without sufficient caregiver education and without demonstrating how aerosol administration should be undertaken. Furthermore, physicians caring for these youngsters often fail to consider alternate, faster, more efficient, simpler to administer and less expensive aerosol therapy using MDIs with valved aerosol holding chambers with masks providing an effective seal to the infant's face. In part, this may be explained by the paucity of pediatric aerosol studies in general and, in particular, the relatively few studies in infants and toddlers. Most studies on the factors determining lung deposition of therapeutic aerosols are based on data from adults or older children, which cannot simply be extrapolated directly to the very young. The evaluation of therapeutic response in this age group is indeed very difficult [2]; hence there are few evidence-based recommendations for aerosol delivery in this age group. We will describe why infants and toddlers are very different with respect to two major issues – namely their anatomy/physiology and their behavior. We suggest possible solutions and future research directions aimed at improving clinical outcomes in this age group.

Anatomical & physiological considerations

The upper airway in infants is quite different from that in adults. The infant larynx is situated much higher in the upper respiratory tract (URT), very close to the base of the infant's tongue [3]. In addition, the epiglottis, which is relatively narrow and floppy, is located nearer the palate. These anatomic differences, as well as the relatively larger caliber of the URT, may partially explain the preferential nose breathing of young infants, as well as the relative difficulty that has been observed when attempting to target aerosols to their lower-respiratory tract (LRT) [4]. The infant pharynx and supraglottic tissue area characteristically are less rigid compared with adults and thus more susceptible to collapse and obstruct the URT, particularly during inspiration.

Infancy is a time of great and rapid changes. The airway caliber in the newborn lung is relatively large compared with the relatively scant parenchyma served. During infancy the volume of the lung parenchyma enlarges more relative to airway volume (i.e., there is a much greater increase in lung parenchymal growth, relative to airway growth throughout childhood) [5]. Thus, the conductance in infant lungs is greater than in older lungs [6]. The significance of this from an aerosol therapeutic perspective remains to be studied. We speculate that once past the URT aerodynamic filter, particles have a greater probability of entering peripheral airways since the distance they must travel is shorter and the dose per unit surface area is greater compared with the adult lung. By contrast, with increasing age, as airway caliber increases towards adult dimensions, particles of similar relatively small size will be carried more readily to peripheral airways when inhaled because the URT aerodynamic filter is less likely to retain the drug particles in the larger airways of adults. Furthermore, the narrower airways of infants are more susceptible to obstruction from any inflammatory airway disease resulting in an additional barrier to aerosol penetration into more peripheral airways.

Infants have a lower inspiratory airflow than older children. Hence, compared with the constant and relatively high (6–8 l/min) flow of aerosol coming from most jet nebulizers, they entrain less air and thus each breath may deliver a proportionally higher dose (more concentrated aerosol) to the younger in than the older child. Normal infants of 6 months to 1 year of age have inspiratory flows that approximate nebulizer output. Thus, the amount inhaled from a nebulizer increases linearly in infancy as the peak inspiratory flow increases to that of the nebulizer and then, beyond infancy, the amount inhaled plateaus, more air is entrained and the dose inhaled per kilogram falls (this may be compensated for by the increased minute ventilation and increased lung deposition in older patients) [7–9].

Implications of nasal breathing in infants

Nasal breathing has been shown to be much less effective in delivering aerosol to the lungs than mouth breathing. This is doubtless related to the high resistance, relatively high flow velocity and turbulence in the nose and nasopharynx, the region of the respiratory tract with the highest resistance, airflow and turbulence [10]. Mathematical models have suggested that under conditions of regular tidal breathing, the nose in infants may be more efficient at excluding foreign materials from the airways compared with adults [4]. Thus, the nose is a very effective aerodynamic filter for potentially noxious as well as therapeutic particles. Unsurprisingly, if the URT is bypassed by aerosol inhalation through the mouth, delivery of medication to the lungs is two- to threefold greater [11].

Laboratory studies have shown that *in vitro* drug delivery is dependent on the choice of impactor inlet, mimicking upper-airway diameter. Drug delivery via an anatomical impactor inlet of a child is much lower than drug delivery via an anatomical impactor inlet of an adult. This *in vitro* finding is in accordance with several radiolabeled lung deposition studies, where for a given inspiratory flow and particle size, lung deposition increases and oropharyngeal deposition decreases with age independent of the inhalation device used. In other words, young children have a low absolute lung deposition and high oropharyngeal deposition although the mass deposited per unit lung volume may be similar to that in adults.

This difference between lung deposition and oropharyngeal deposition may be further explained by the characteristics of breathing patterns in young children – in particular, low tidal volumes and a high respiratory rate. It has been shown that lung deposition decreases with high respiratory rate and/or high inspiratory flow [12,13]. Relatively high inspiratory flow velocity, especially when nose breathing, will lead to increased impaction of aerosol particles in the URT, resulting in a lower dose to the lungs [13].

In summary, based on the large differences in breathing patterns and airway anatomy, it is evident that the lung targetable fraction of an aerosol for infants and young children is less than

that of older children, adolescents and adults, although the dose per unit volume may be similar, accounting for the fact that infants usually require a range of ex-aerosol generator doses similar to adults.

Lung deposition in various diseases in infants

The principal mechanisms accounting for drug deposition within the respiratory system are impaction and sedimentation [14,15]. High inspiratory flows favor impaction of particles in the URT. This is particularly the case with larger particles (mass median aerodynamic diameter [MMAD] 3–5 µm). The smaller the particles and the lower the inspiratory flow velocity, the greater is their probability of avoiding impaction and bypassing the URT to deposit, mainly by sedimentation, in the LRT. Gravitational sedimentation of smaller particles within the LRT also occurs more slowly and, thus, in adults is facilitated by breath holding. Since infants are unable to hold their breath, a greater proportion of the inhaled medication is likely to be exhaled.

By labeling aerosol particles with appropriate radioactive agents (e.g., ^{99}Tc) it is possible to trace deposition patterns. Although the risk is extremely small [16], there are obvious ethical concerns that have limited the use of these studies in pediatrics. Thus, only sparse information on lung deposition in infants is available.

The results from the few available deposition studies are strikingly similar and summarized in Table 1. For example, Mallol *et al*. found that lung deposition in five infants with cystic fibrosis (CF) was 2.0 ± 0.7% of the nebulized dose [17], Chua *et al*. found lung deposition of 1.3% in 12 infants with CF [11], and Fok *et al*. found lung deposition of 1.74 ± 0.21% in 13 infants with bronchopulmonary disease [16]. With increasing age, mean total lung deposition increases to 5.4% in 2–4-year-old children and to 11.1% in 5–7-year olds [19], values similar to those in adults [20]. The results of a recent study in infants with acute bronchiolitis were remarkably similar to those obtained in infants with other obstructive airway diseases even though the latter were in clinically 'stable' condition and had a somewhat different disease [21]. Not only was the total lung deposition fraction in the bronchiolitis study similar, but the regional lung distribution of radiolabeled aerosol was also similar with a marked predominance of central-airway deposition. This is in contrast to normal adults and, increasing with age, in children, in whom there is a shift towards greater peripheral deposition starting as young as 2.5 years of age [19].

Taken together, these observations suggest that the major patient-related factor determining and/or limiting LRT aerosol deposition in this group of patients may not be simply their clinical status but rather their underlying anatomy and resulting pathophysiology. That is, for a given inflammatory response, the anatomically narrower airways of infants develop much greater airflow obstruction due to edema, secretions and bronchospasm because the resistance to airflow is proportional to the third or even fourth power of the much smaller initial diameter. Thus, the factors limiting peripheral airway aerosol delivery in infants may be magnified compared with those in older children and adults.

Compared with the lung dose, almost three-times as much drug was deposited in the URT and gastrointestinal tract (GIT) in infants with bronchiolitis [21]. This is in sharp contrast to adults and even young children with stable asthma where the URT and GIT fraction is relatively much lower [19]. This can be explained by the greater respiratory rate of infants with bronchiolitis causing more URT impaction [16]. Furthermore, they probably also exhale more aerosol (due to the short particle residence time) and have greater nasal aerodynamic filtration [11]. The consequence of increased URT and GIT aerosol deposition is increased systemic absorption, which may result in side effects such as β-agonist treatment-related tachycardia. It is possible that some clinical effects (e.g., oxygenation or respiratory rate) are mediated, in part, by systemic levels of β-agonist absorbed from the URT and GIT, as well as from the conducting airways. These may also result, in part, from redistribution of the medication from proximal to more peripheral airways via the endobronchial circulation, a mechanism that has been postulated to explain the rapid response to inhaled bronchodilator therapy in acute, severe asthma in adults [22]. It would be of interest to compare the intrapulmonary dose and distribution of radiolabeled aerosol, pharmacokinetics and the clinical and physiological responses to both large and small size β-agonists and steroid aerosols in respiratory syncytial virus (RSV) bronchiolitis in infants to try to resolve some of these questions and improve our understanding of the role of the endobronchial circulation.

It must be remembered that all of the data in this section on lung deposition and the potential mechanisms determining treatment outcomes in infants are not necessarily generalizable other than to the specific settings of these studies. These studies were all conducted under the supervision of medical personnel to ensure a tight facemask seal. The factors pertinent in real life, but infrequently studied, are much more relevant to general pediatric practice and are, for the most part, related to infant cognitive skills, behavior, compliance and acceptance of treatments, as well as the ability of parents and other caregivers to actually carry out the therapeutic regimen prescribed and hopefully taught to them by healthcare providers. These factors will now be discussed.

Table 1. Lung deposition in various diseases in infants.

Author	Disease	Mean age (months)	n	Lung deposition (%)	Ref.
Chua *et al.* (1994)	CF	9	12	1.3	[11]
Mallol *et al.* (1996)	CF	12	5	2.0	[17]
Fok *et al.* (1996)	BPD	3	13	1.7	[18]
Wildhaber *et al.* (1999)	Asthma	33	8	5.4	[19]
Amirav *et al.* (2002)	Bronchiolitis	8	12	1.5	[21]

BPD: Bronchopulmonary disease; CF: Cystic fibrosis.

Aerosol therapy in the 'real world': behavioral aspects

In our opinion, in addition to the previously discussed physiological and anatomical differences, the most important factor determining the aerosol dose delivered to infants and small children is their behavior and their and the caregiver's compliance/adherence with aerosol therapy. In this regard, the caregiver's administration of the daily dose prescribed, the facemask fit, crying during aerosol administration and general acceptance of treatment are the most crucial factors to consider under real-life conditions.

Facemasks

It is not until 3–4 years of age that children develop sufficient understanding to consistently and effectively inhale through a mouthpiece [1]. Consequently, a well-fitting facemask should be used in this age group as the potentially most efficient interface between the aerosol generator and the patient, a fact that has been fully appreciated only fairly recently. Studies have shown that comfortable masks providing a good seal are a prerequisite for 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, with a small-volume nebulizer, even a 1-cm gap between the mask and the face reduced the dose delivered by 50% [23]. We and others have recently compared the effectiveness of the seal of various facemasks and demonstrated the effect of the facemask seal on aerosol delivery [24–26].

Any gap between the mask and the face leads to greatly reduced drug delivery efficiency particularly when administering aerosol therapy to infants and children by means of MDIs with VHCs since little or no drug is delivered to the respiratory tract unless the infant is actually inhaling through the device. With jet nebulizers, a poor seal between the mask and face results in continuous leakage of drug aerosol throughout the respiratory cycle, as well as entrainment of fresh air that dilutes the aerosol dose. Furthermore, with newer breath-actuated nebulizers, no aerosol will be produced during inspiration unless the mask is well sealed to the face. Frequently, facemasks available for infants and young children have been merely smaller versions of those used for adults with little consideration given to their special needs [1].

The importance of facemasks was highlighted in a recent special symposium summarizing some *in vitro*-related studies [27–29] and was reviewed by us more recently [30].

The importance of the facemask fit in day-to-day clinical practice has also been demonstrated by Janssens *et al*., who showed increased variability with the poorly fitting mask supplied with the NebuChamber® VHC [31]. We recently improved the performance of the NebuChamber by developing an improved mask with a much better seal that increased the delivery efficiency of therapeutic aerosols in young children by 30% [32]. It was subsequently used successfully in a study of infants and young children with acute asthma presenting to an emergency department [33]. A similar attempt to improve the facemask fit in clinical settings was reported by Esposito *et al*. who attached a different round facemask to the NebuChamber [25].

Surprisingly, both in our study and in that of Esposito *et al*., the dose variability did not benefit from the improved mask, but instead increased with decreasing cooperation by the children. This leads us to suggest that while the mask configuration is indeed extremely important for determining the aerosol dose delivered, it is probably less important than the magnitude of the daily variation, which probably depends mainly on the caregiver's attention to optimal mask fit and the infant's cooperation.

The effect of crying on the mask-to-face seal is complex. It is suggested that infants' resistance to the mask, caused by fear of being smothered, accounts for their crying and squirming. This in turn results in a vicious cycle potentiated by excessive force applied by increasingly frustrated caregivers in order to achieve an effective seal between the mask and the face of the child [34]. Indeed, it has previously been suggested that the most common cause of a poor seal is crying and/or distress associated with the treatment [35]. Which is the cause and which the effect, and how common is crying? Ritson *et al*. suggested that the requirements for a seal in their patients induced distress and affected the efficiency of aerosol delivery [36]. Similarly, Marguet demonstrated that crying occurs in a significant proportion (38%) of her young patients receiving inhaled therapy administered while they are awake [37].

Crying during aerosol administration by means of a mask is very common in the awake infant. In our experience, crying during mask administration is not inevitable if the child is well prepared in advance by making a relaxed game out of fitting the mask onto both the face of the caregiver and that of the child, best undertaken prior to the time that the child actually needs treatment. Parents should be given guidance on ways to help their child accept the medication. Allowing the child to hold and play with the delivery device on several occasions may 'acclimatize' the infant to the mask. An infant or toddler can then hold the mask up to the parent's face or to the 'face'

Table 2. Behavior and lung deposition.

Author	Mean age (months)	Deposition during crying (%)	Deposition without crying (%)	Ref.
Tal *et al.* (1996)	15	0.3	2.0	[38]
Murakami *et al.* (1990)	0–24	Neglible	Unknown	[39]
Wildhaber *et al.* (1999)	24	1.3	5.4	[19]
Iles *et al.* (1999)	13	0.1*	0.4*	[40]
Amirav *et al.* (2003)	8	High URT–GIT	Low URT–GIT	[41]

*By urine analysis.
GIT: Gastrointestinal tract; URT: Upper respiratory tract.

of a favorite doll or stuffed animal and then finally place it on their own face themselves. With longer small-volume wet nebulizer treatments, distracting and rewarding children with a special video may also be helpful.

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 quiet brief inhalation. During nebulizer treatment, the aerosolized drug is unavailable during exhalation and during a very fast inhalation, inertial impaction of the inhaled medication makes it more likely that the aerosol will deposit mainly in the URT than in the LRT. Patient agitation also makes it less likely that there will be a good seal with the facemask.

Only anecdotal information is available regarding the relationship between behavior of the infant during aerosol therapy and respiratory tract deposition (Table 2) as a randomized control trial would be virtually impossible. Tal *et al.* reported that lung deposition during crying in two of their 15 infants who inhaled MDI-generated salbutamol from a VHC (AeroChamber®, Trudell Medical International, ON, Canada) with mask was only approximately 0.35%, in contrast to a mean of 2.0% when they were breathing quietly [38]. Murakami *et al.* also reported that lung deposition in crying infants using a nebulizer and mask was negligible (scintigraphic data were provided for only one patient) [39]. Wildhaber and colleagues recently described their experience with one crying child whose lung deposition was markedly reduced compared with his 16 noncrying peers [19]. Moreover, the gastrointestinal deposition in this patient was 50% higher than the rest of the group with a sevenfold increase in the ratio of gastrointestinal (from swallowed aerosol medication) to lung deposition. Iles *et al.*, using urinary excretion of the drug, also showed a fourfold reduction in lung deposition when infants were crying [40].

We recently demonstrated a clear relationship between infants' distress and deposition of aerosol in the URT that was subsequently swallowed and detected in the GIT [41]. The more distressed the infants were, the more aerosol was deposited extrathoracically.

Schüepp recently combined some of these factors and demonstrated scintigraphically that there was relatively poor deposition with an inadequate seal or with crying (note major upper airway deposition) versus improved deposition with a good seal and even better deposition when the particles were smaller (Figure 1) [42]. A recent elegant *in vivo* study by Nikander *et al.* demonstrated that crying reduced the inhaled mass to 1% of the label dose [43].

Given these results it is clear that aerosol delivery to the lungs of crying children is not enhanced as a result of a deep inspiratory breath. This is probably because crying or screaming infants adopt abnormal breathing patterns [44] characterized by greatly prolonged expiration followed by short, high inspiratory flow velocity gasps leading to greater aerosol impaction in the throat and frequent swallowing. While increased bronchodilator deposition in the URT and GIT may be compensated for by increased dosages, this observation may be of greater concern during nebulizer or MDI with VHC treatments with corticosteroids due to reduced benefit, increased systemic absorption and a greater risk of adverse effects [45].

Thus, in contrast to previous assumptions, crying is now known to be detrimental and all efforts should be made to avoid it during aerosol administration.

So where do we go from here? Alternatives & solutions

There is clearly a need to develop more acceptable and patient-friendly methods for improving aerosol delivery to infants [46]. We will mention just a couple of interesting developments that will probably be further explored in the near future. These relate to blow-by treatments, sleep, hood-based delivery and the issue of smaller particles.

Blow by

In despair, many parents resort to mask-free aerosol delivery techniques, thus aiming to avoid struggling with their baby during therapy. This has led to the common practice of blow-by aerosol delivery using a mask held near the child's face. The amount of drug delivered to babies using blow by is negligible [23] and this practice should be abandoned. A recent *in vitro* study confirmed its marked inefficiency [47].

However, two more recent *in vitro* studies performed by Geller showed that when blow by is delivered via an extension tube, the results were as good as a tightly fitting mask [48,49]. These surprising results are probably the result of more concentrated delivery of aerosol near the nose and mouth. Although these results were reproduced recently by Lin *et al.* [50], they will need confirmation *in vivo*.

Sleep

Sleep is another fascinating area of future research. Compared with being awake, sleep is associated with more regular breathing, lower breathing rate and lower inspiratory flows [51–53], factors that improve aerosol delivery to the LRT. Administration of inhaled drugs to infants during sleep may therefore be a good alternative for uncooperative toddlers. Such efforts have been attempted by a recent *in vitro* study by Janssens *et al.* [54]. Janssens recorded the breathing patterns of awake and sleeping babies, ran them on a breathing simulator and showed that treatment during sleep greatly improved VHC aerosol delivery and doubled the lung dose compared with the awake state.

In an earlier *in vivo* study, Murakami demonstrated in seven sleeping infants that scintigraphic deposition of nebulized aerosol appeared significantly better compared with when they were awake. The mean deposition during sleep appeared to be as good as that in cooperative, older (3–14 years) awake children. However, sleep was induced, thus it was not a real-life study.

These promising results were somewhat contradicted during attempts to translate these *in vitro* improvements to real-life situations. Noble *et al.* showed that although mask VHC aerosol

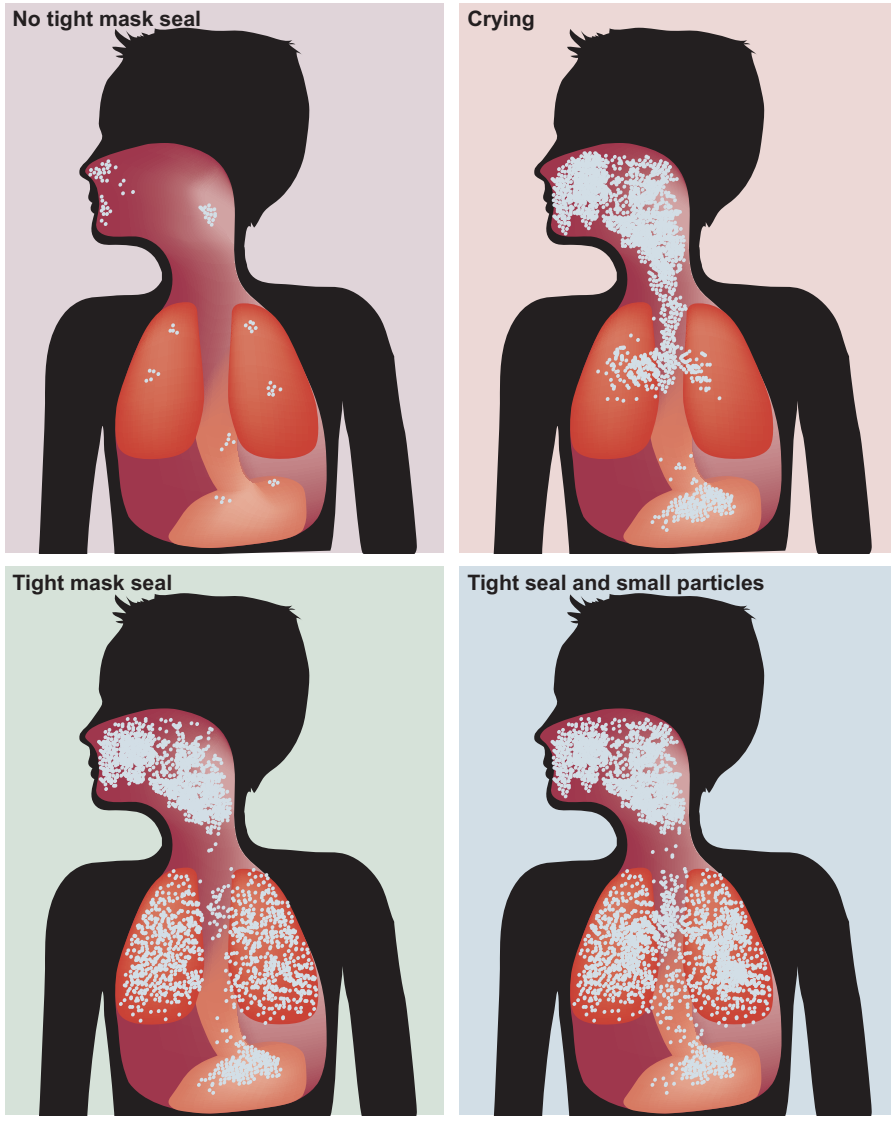

Figure 1. The effects of mask seal, crying and small-particle inhalation on lung deposition.
Modified with permission from [42].

administration during sleep was successful in most infants and toddlers, a subgroup (17%) of the patients wake during the procedure [55]. In a more recent study, which directly assessed the effects of sleep on aerosol delivery by VHC, it was found that 70% of infants woke up during application of the mask and most of them (75%) became distressed. The delivered dose in this case was almost half of the awake state [56]. Thus, aerosol administration during sleep is better – providing that you do not wake the baby!

The supine position may have some advantage as it has been shown that in adults, lung deposition in the supine position was more homogeneous throughout the lung compared with the upright position [57,58]. It is unknown whether this would be the same for infants although that would be less likely since the 1:1.3 apex–base increase in ventilation shown scintigraphically in seated adults has been related to the 25–30-cm vertical height of the lungs in the upright position associated with an approximately 1:3 mass of blood per unit volume of lung from apex to base – postulated to be due mainly to gravity on the blood column in the low-pressure pulmonary circulation [59]. In infants, these differences would be expected to be much less due both to their lung dimensions and because aerosol administration by caregivers would usually be carried out in the semirecumbent position if infants are not recumbent in their crib.

Hood

Some recent studies have suggested considerable potential for hood-based aerosol delivery to infants, thus avoiding the application of a facemask.

A study carried out in the Pediatric Department, Ziv Medical Center (Safed, Israel) compared the lung deposition efficiency of nebulized aerosol delivered by facemask or via a prototype hood [41]. At random, 99M Tc albuterol solution was administered by nebulizer plus mask or hood to 14 wheezy infants (mean age 8 ± 5 months). The dose and distribution of albuterol were evaluated using γ-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 = not significant). Variability with the mask was greater than with the hood (coefficient of variance = 54 vs 39%; p = 0.01). Both treatments provided similar clinical benefit and physiological outcomes, as reflected in improved oxygen saturation, reduced respiratory frequency and increased heart rate. Infants accepted the hood much better than the mask. The hood was associated with significantly less patient distress (mean behavioral index of 1.3 during hood vs 3.4 during mask treatments; p = 0.01) and significantly greater parental preference compared with the facemask (hood preferred by 12 parents [86%; p < 0.01], mask by one and no preference by one). There was a positive correlation between poor acceptance and upper airways and stomach deposition for both treatment modalities.

As nothing comes into contact with the infant's face, this mode of administration is less likely to cause anxiety and, therefore, less crying. Not surprisingly, the hood was preferred by a significant majority of in-hospital infant caregivers in another recent study [60]. In that double-blind placebo-controlled study the hood was as effective as a conventional facemask for delivering nebulized hypertonic saline with adrenalin to infants

hospitalized with RSV bronchiolitis. 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 nebulizer (Aerogen Corporation, CA, USA), which uses an electronic vibrating disc micropump technology [47]. In this study, the Aeroneb nebulizer plus hood delivered 3.6% to the lung, 50% more than either VixOne™ jet nebulizer plus hood or VixOne jet nebulizer plus tight fitting mask. Care should be taken to ensure the optimal position of the nebulizer within the hood [61,62].

Administration of smaller particles

As noted previously, the dose of medication reaching the bronchiolar region in infants might be mostly limited by their normally small airway caliber if the aerodynamically large aerosol particles generated by most inexpensive, small-volume jet nebulizers, common to clinical practice, are used. In this regard it is worth emphasizing that aerodynamic size is proportional to the cube of the droplet diameter so that a typical jet nebulizer-generated MMAD 3–4-µm aerosol would behave aerodynamically like particles 27–64-times larger than that of an identically formulated 1-µm aerosol. Aerosol generation and delivery factors influencing aerosol deposition include nebulizer performance, which may be expressed as total drug mass output per unit of time, and aerodynamic particle size. Nebulizers that produce a greater mass output, mainly in the fine particle fraction (MMAD < 3 µm and more specifically in the 1–2-µm range) provide considerably more efficient LRT deposition, mainly because less aerosol is trapped by aerodynamic filtration in the nebulizer, tubing and URT. In keeping with their much smaller airways, further narrowed by airway inflammatory edema and hypersecretion in inflammatory airway diseases, the particle size necessary for efficient aerosol drug targeting to the smaller airways of the LRT in infants should probably be much smaller than that for older children and adults. Further studies are needed in a number of conditions characterized by airflow obstruction and pulmonary parenchymal diseases using formulations and/or devices that produce such particles. In this regard, particle-size selective VHCs, such as the AeroChamber, remove approximately 90% of a normal saline aerosol over 2.8 µm [63] and reduce the URT dose of MDIs approximately 90% and total body dose approximately 70% by providing polymeric MDI-generated albuterol aerosols of MMAD about 1.8 µm. Since this would considerably improve the therapeutic ratio, much larger doses of bronchodilator medication could be targeted safely to the 1–2 mm peripheral airways. Furthermore, with the recent introduction of MMAD 1.1 µm beclomethasone dipropionate pMDI solution aerosol (QVAR®, 3M Pharma, MN, USA) the hypothesis that smaller aerosol particles might provide greater therapeutic benefit in bronchiolitis could be tested [64].

Mallol *et al*. demonstrated that lung deposition in CF infants more than doubled using small (MMAD 3.6 µm) versus large aerosol particles (7.7 µm) [17]. In two recent *in vitro* studies using an infant upper-airway model, Janssens *et al*. have shown that the use of small particles up to the size of 2.1 µm improves the dose delivered to the lungs substantially [13,65].

As described previously, Schüepp scintigraphically demonstrated a marked improvement in lung deposition when using small aerosol particles [42,66]. Owing to the very large fraction of particles under 2 µm, which make deposition relatively independent of inspiratory flow or breathing patterns, it is likely that extra-fine therapeutic aerosols would be more effective for treating infants.

Clearly, there is a need for additional studies with drug particles in the order of MMAD 1–2 µm in order to better determine the potential benefit of improved targeting of aerosols to infants' peripheral airways and lung parenchyma.

Expert commentary

In this review we have discussed how infants and toddlers are different with regard to aerosol delivery, as well as anatomical and physiological issues unique to children under 2–3 years of age. We highlighted the crucial importance of their behavior in achieving aerosol delivery and, finally, we suggested possible solutions and future research directions aimed at improving clinical outcomes in this age group.

Five-year view

During the next 5 years we will expand our understanding of the major factors influencing the targeting of therapeutic aerosols to infants and young children. Improved understanding will lead to the development of better aerosol delivery devices more suited to the unique needs of infants and toddlers.

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Key issues

- When drugs are delivered to infants and toddlers, it should be remembered that they are not young adults.
- Infants have unique anatomic, physiologic and emotional characteristics that make them a very unique population for aerosol therapies; thus, aerosol delivery systems must take into account the special needs and respiratory characteristics of infants and toddlers.
- The notion that crying is good for aerosol delivery is a myth that should be rejected. Measures should be taken to make aerosol delivery systems more infant and toddler friendly in order to minimize crying during aerosol administration.
- Aerosol delivery devices should take into account the special needs and characteristics of infants and toddlers.

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