Measurements of deposited aerosol dose in infants and small children

Timothy E. Corcoran[1,2,3]

[1]Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA; [2]Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA, USA; [3]Department of Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburgh, PA, USA

Correspondence to: Tim Corcoran, PhD. UPMC MUH NW628, 3459 Fifth Ave, Pittsburgh, PA 15213, USA. Email: corcorante@upmc.edu.

Abstract: Pediatric patients are very dependent on inhaled aerosol medications. There are significant differences in how these aerosols deposit in the lungs of children *vs.* adults that may affect the efficacy of the therapies. Inefficient aerosol delivery to children, caused by factors such as high mouth and throat deposition during oral inhalation, significant losses within adjunct devices such as masks, and high rates of nasal deposition during cannula delivery, can lead to dosing that is difficult to control. Here we discuss the methods, such as deposition scintigraphy, that are used to assess inhaled dose *in vivo* and review previous studies where these techniques have been applied to measure dosing in children. This includes studies of nebulizers and metered dose inhalers and delivery through adjuncts such as facemasks and nasal cannulas. We discuss the factors that can lead to inefficient inhaled drug delivery and high levels of mouth and throat deposition in children. Finally, we propose areas of innovation to improve inhaled drug delivery to this population. There is a need for child-specific technologies for inhaled drug delivery. This includes the use of smart devices that can guide pediatric breathing patterns and better engage children during treatments, the use of smaller aerosols which are less likely to deposit in the upper airways after inhalation, and the design of better nasal cannula interfaces for aerosol delivery to infants.

Keywords: Pediatric; nebulizer; metered dose inhaler; scintigraphy

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Introduction

Pediatric patients with lung disease depend on inhaled medications. This includes bronchodilators and corticosteroids for asthma and childhood wheeze, racemic epinephrine for croup, and antibiotics, hypertonic saline, and mucolytics for cystic fibrosis (CF). These medications are delivered from metered dose inhalers (MDIs), dry powder inhalers (DPIs), and medical nebulizers. Aerosol deposition can vary significantly between children and adults based on differences in airway size and respiratory parameters. Children also vary in their ability to cooperate with treatments and may require delivery system adjuncts such as masks or nasal cannulas. These factors can lead to significant dose variability and potentially affect the efficacy of inhaled therapies. Here we will discuss the techniques used to study aerosol dosing *in vivo*, review available studies that have measured aerosol dose in children, discuss the factors that adversely affect aerosol dosing for children, and consider potential methods for improving aerosol drug delivery to infants and children.

Techniques for studying aerosol dosing in children

Deposition scintigraphy techniques are used to measure the dose of aerosol medication delivered to the lungs during inhaled therapy treatments (1-3). These studies utilize a radiopharmaceutical that is directly or indirectly labeled to the active drug component of the inhaled medication. Pre-clinical studies are performed to establish a labeling method that provides a direct relationship between

radioactive counts emitted by the radiopharmaceutical and the active drug dose. Once this relationship is validated across different aerosol size classes (4), radiation can be used as a quantifiable analog of drug dose. It can easily be measured in aerosol delivery systems and leakage/exhalation filters before and after administration to determine total delivered dose [An example of the use of this "mass balance" technique pediatric subjects can be found in (5)]. With the incorporation of gamma camera imaging, radiation measurements can also be used to quantify deposited dose within the mouth, upper airways, lungs, esophagus, and stomach, using 2D or 3D imaging. These studies can be performed with nebulizers (6), metered dose inhalers (7), dry powder inhalers (8), and condensate aerosol delivery systems (such as electronic cigarettes) (9).

These techniques have been applied less frequently in children and infants, largely based on the radiation exposure associated with their use. However, the use of careful technique can limit radiation exposure, and good images can be attained with deposited lung doses in the range of 1.5 MBq (40–50 µCi) using Technetium 99m based compounds. Technetium 99m has a relatively short half-life (~6 hours) and is available forms that are readily cleared from the body. The risk to benefit ratio associated with this exposure may be favorable in pediatric populations that are significantly dependent on inhaled medications, where patient-specific or generalizable knowledge on dosing is important to improving clinical care. Nuclear medicine techniques are commonly performed in children, including infants, and dosimetry tables for estimating inhaled exposures are available (10).

Aerosol deposition studies in infants and children

Nebulizers

O'Doherty *et al.* measured the lung doses of nebulized pentamidine delivered to 12 children with HIV. The percent of the nebulized dose deposited in the lungs was 5.5%±2.4% for children ages 8–11, 7.2%±2.2% for ages 12–15, and 7.1%±2.6% for adults (± SD) (11).

Chua *et al.* measured aerosol deposition from medical nebulizers in 12 infants and 8 children with cystic fibrosis. The 12 infants ranged in age from 0.3–1.4 years old. All were anesthetized during aerosol delivery and a mask was utilized. In the infants, deposited lung doses ranged from 0.3–2.1% of nebulized dose. Deposited head/upper airway doses ranged from 38.8–84.7%. Lung doses after oral inhalation in children from 6–12 years old ranged from 5.3–9.1%. Upper airway doses in that group ranged from 30.1–49.4% (12).

Mallol *et al.* studied aerosol deposition in 20 infants with cystic fibrosis considering the use of different sized nebulized aerosols and sedation *vs.* no sedation. Non-sedated infants inhaling a 7.7 µm aerosol deposited 0.76%±0.36% (n=5) of the loaded dose in their lungs *vs.* 2.0%±0.71% in a group of infants inhaling a 3.6 µm aerosol (P<0.01, ±SD). Oropharyngeal deposition was 6.78%±2.72% *vs.* 2.4%±0.83% in the same groups (P<0.05). Sedation did not significantly affect aerosol deposition (13).

Fauroux *et al.* compared the delivery of nebulized aerosols with and without pressure support in children and adults with cystic fibrosis, ages 6–21. Lung deposition was 15.3%±8.3% (of nebulized dose) with pressure support *vs.* 11.5%±5.7% without (P<0.05 through a paired comparison). When considered based on percentage of loaded dose: 2.4%±1.5% *vs.* 1.7%±1.2% (P=0.01) (14).

Schueepp *et al.* measured aerosol deposition in 10 asthmatic children, ages 0.5–3 years using budesonide with Technetium 99m-DTPA added. The solution was delivered using a vibrating mesh nebulizer and a facemask. Lung deposition varied from 8–56.4% of emitted dose. Oropharyngeal dose (including facial deposition) varied from 43.6–92.0%. The study did not differentiate dose on the face from dose in the mouth (15).

Amirav *et al.* measured aerosol deposition in 12 infants (<12 months old) comparing delivery with a nebulizer and mask to a nebulizer + mask + pacifier combination. Mean right lung deposition (± SD) using a mask with attached pacifier was 1.6%±0.5% which was similar to deposition with a conventional mask: 1.7%±0.9%, P=0.81. Stomach doses were 1.2%±1.2% and 2.0%±1.9% respectively. Upper airway doses were 3.7%±1.3% and 2.0%±1.9% (16).

Corcoran *et al.* measured the distribution of nebulized Technetium 99m sulfur colloid aerosols delivered by nasal cannula to 18 infants with congenital heart defects who were performing research mucociliary clearance scans. Increases in the percentage of the drug delivered to the lungs *vs.* the nasopharynx were achieved using lower nasal cannula air flowrates (0.2 L/min). The fraction of the deposited in the lungs was 33.5%±13% at 0.2 L/min *vs.* 4.5% ±2.2% at 2 L/min of cannula flow (± SD). The remaining fraction of the deposited dose was found in the nasopharynx (17).

Metered dose inhalers

Tal *et al.* measured the dose of Technetium 99m labeled salbutamol delivered by metered dose inhaler and deposited in the lungs of 15 infants and children with asthma, cystic fibrosis, or bronchopulmonary dysplasia. The average deposited dose was 1.97%±1.4% in the lungs (% of emitted dose ± SD), 1.28%±0.77% in the oropharynx, and 1.11%±2.4% in the stomach. The remainder of the dose was lost in the spacer (18).

Devadason *et al.* measured the deposition of Technetium 99m-labelled beclomethasone HFA (QVAR™) delivered from a breath-actuated metered dose inhaled (Autohaler™) to 16 children ages 5–14 with mild asthma. Lung deposition was 36.9%±9.2% (% of emitted dose ± SD) in 5–7 years old children *vs.* 46.5%±11.6% in ages 8–10 and 54.1%±10.7% in ages 11–14. Oropharyngeal + GI deposition was 59.7%±8.2%, 48.9%±12.3%, and 40.3%±11.8% for the respective age groups. They demonstrated that lung dose increased with FEV1 and FVC and that mouth and throat deposition decreased with FEV1, FVC, height and age. Lung doses in older children (11–14 years) were similar to reported doses from adults (5).

Roller *et al.* also measured the deposition of Technetium 99m-labelled beclomethasone HFA (QVAR™), delivered from a metered dose inhaler plus spacer to 24 children with asthma. The authors reported a median size of the aerosol of 1.1 μm. Half of the group inhaled the drug using 5 tidal breaths while the other half used slow inhalations followed by a breath hold. Lung deposition in the tidal breathing group was 35.4%±18.3% (% of emitted dose ± SD) in 5–7 years old children *vs.* 47.5%±13.0% in ages 8–10, and 54.9%±11.2% in ages 11–17. For the same age groups using slow inhalations and breath holds, lung deposition was 58.1%±6.7%, 56.6%±5.2% and 58.4%±9.2%. Oropharyngeal + GI deposition was 24.0%±10.5%, 10.3%±4.4%, and 10.1%±6.2% using tidal breathing, *vs.* 12.9%±3.2%, 20.1%±9.5%, and 20.8%±8.8% with slow inhalations and breath holds. Spacer losses were 40.2%±9.2%, 41.5%±15.1%, and 30.7%±11.5% with tidal breathing *vs.* 24.1%±7.0%, 18.2%±1.6%, and 20.3%±4.5% with slow inhalations and breath holds (19).

Erzinger *et al.* measured the deposition of salbutamol aerosols from a metered dose inhaler and a nebulizer in recurrently wheezy children. All delivery was done by facemask. Pulmonary deposition (% of loaded dose ± SD) was 7.4% in 31 male subjects using the metered dose inhaler *vs.* 8.2% in 36 male subjects using the nebulizer. In these same subjects, GI deposition was 12.2% *vs.* 10.1%, deposition on the face was 5.2% *vs.* 3.6%, and mask losses were 4.4% *vs.* 0.8%. Any amount of face mask leak or screaming by the children caused significant decreases in pulmonary dose (20).

Fok *et al.* compared drug delivery from nebulizers and metered dose inhalers in ventilated and non-ventilated infants with bronchopulmonary dysplasia (BPD). Delivery was via facemask (nebulizer) or facemask + spacer (MDI). Delivery for the ventilated infants was done in line. Lung dose in the non-ventilated subjects was 0.67%±0.17% for the MDI and 1.74%±0.21% for the nebulizer (% of actuated dose/% of nebulized dose, ± SEM). In ventilated infants: 0.98%±0.19% (MDI) and 0.95%±0.23% (nebulizer) (21).

Factors adversely affecting aerosol dosing to pediatric patients

Aerosol mechanics in the pediatric airway

Impaction and sedimentation are the primary mechanisms that cause aerosol deposition in the airways and the lung. Impaction occurs when aerosol droplets acquire too much momentum to follow airflows through changes in direction or velocity and instead move in straight line paths that cause them to collide with surfaces. The tendency for impaction increases with aerosol density and size and airflow velocity and decreases with air viscosity and the size of the airway. These factors can be collected into a single dimensionless quantity called the Stokes number which considers the ratio of the inertial force of the aerosol to the viscous steering force of the airflow:

$$\text{Stokes} = \rho d^2 V / 18 \mu D \quad [1]$$

Where ρ is the density of the aerosol, d is aerosol diameter, V is air velocity, μ is air viscosity, and D is airway diameter. A slip correction factor may be added to the numerator when applied with very small aerosols (22). High Stokes numbers are associated with increases in inertial aerosol deposition, especially in regions with high air velocities where flows change direction (back of the mouth, carina, upper airway bifurcations, etc.). *Table 1* shows the estimated Stokes numbers for 5 and 3 μm aerosols based on the respiratory characteristics and airway diameters of adults and children of different ages. It demonstrates the trend towards higher Stokes numbers in pediatric subjects which are likely to be associated with higher levels of mouth, throat, and upper airway

Table 1 Stokes numbers calculated for pediatric and adult subjects, based on tracheal diameter, for 3 and 5 μm aerosols. The Stokes number is the ratio of the aerosol inertia to the steering forces of the inhalation airflow {Eq. [1]}. Increased Stokes numbers are associated with an increased likelihood of inertial deposition in the mouth, throat, and upper airways. High rates of mouth and throat aerosol drug deposition are often seen in pediatric subjects

Age (years)	Inhalation Flowrate (L/min)	Tracheal diameter (cm)	Stokes (5 μm) ($\times 10^{-3}$)	Stokes (3 μm) ($\times 10^{-3}$)
18	19	1.6	7.3	2.6
8	12	1.2	11	3.9
3	7	0.9	16	5.7
1	5	0.7	21	7.5

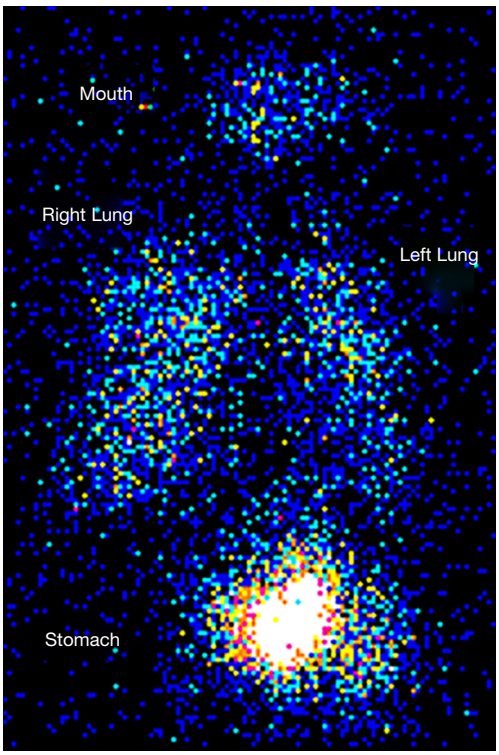

Figure 1 Nebulized aerosol deposition in an 8-year-old child with Cystic Fibrosis depicted using nuclear imaging techniques. The majority of the dose was deposited in the mouth and swallowed into the stomach.

deposition.

High rates of mouth and throat aerosol drug deposition have often been demonstrated in pediatric subjects. *Figure 1* shows an aerosol deposition scintigraphy image that depicts deposited aerosol in the mouth, lungs, and stomach of an 8-year-old child after a nebulizer treatment. The high levels of stomach activity are associated with aerosol dose deposited in the mouth that has been subsequently swallowed. These effects are likely to explain increased aerosol losses in the mouths and throats of pediatric patients when compared to adult subject.

Interfaces

Facemasks are often used to deliver aerosols to infants and younger children. Losses to the environment, within the mask, and onto the patient's face are inherent with the use of these devices. These losses can contribute to low dosing efficiency and significant variability in dosing. *In vitro* studies using the Sophia Anatomical Infant Nose-Throat or SAINT model demonstrated deposited lung doses of 7.17%±0.01% *vs.* 11.42%±0.01% losses in the mask and 71.99%±0.02% losses to the environment (23). The design of the mask and the quality of the seal will significantly affect performance (24-26).

Nasal cannula systems have been considered for aerosol delivery to infants. Nasal cannulas are often used in the pediatric critical care with high gas flowrates to provide oxygenation and potentially airway support as well. Several *in vitro* studies have demonstrated the viability of delivering aerosol through cannulas (27,28), however, several *in vivo* studies have demonstrated high rates of deposition within the nose when these systems are used that limit pulmonary delivery (17,29). Nasal deposition may be caused by direct impaction of the aerosol at the nasal valve or by the accumulation of aerosol-laden gas within the nasal cavity. Accumulation occurs when the rate of cannula gas delivery exceeds the minute volume being drawn into the lungs and results in aerosol deposition throughout the nasal cavity which has extensive internal surface area. This deposition can be limited by using decreased cannula flowrates (17,30). However, these flows are well below those used to provide oxygenation.

Cooperation

Child distress and the level of cooperation provided during the treatment can significantly affect the dose delivered during inhaled therapy. Crying and screaming have both been shown to significantly decrease dosing (15,20). As children become older and begin self-administration, the child's level of attention to the treatment must also be considered, especially for longer nebulizer treatments. Frequent withdraw of the nebulizer from the mouth or nose breathing will limit dose.

Improving aerosol delivery to pediatric subjects

There are significant opportunities to improve inhaled drug delivery to pediatric subjects. High rates of oropharyngeal deposition could potentially be controlled using smaller or less-dense aerosols. Some groups are exploring the use of hygroscopic aerosols that are very small when delivered through the nose but grow within the humid environment of the lungs, allowing for effective sedimentation and deposition in target lung zones (31,32). Efficiency might also be further increased through the use of controlled breathing patterns that limit inhalation velocity, increase tidal volume, deliver aerosol only during specific portions of the breath (bolus delivery), or incorporate slight breath holds (33-35). Incorporation of such controls will be more feasible as more "smart" devices with onboard processors become more available (36). Such devices may also be useful for better engaging children during aerosol therapies through games or other interventions in order to maintain focus and optimize delivery. Previous *in vitro* studies provide equations that can be used to predict pediatric upper airway deposition and the relative effects of changes in delivery system design (37). Empirical correlations for predicting airway size by age are available (38). Experimental apparatuses for pre-clinical testing of aerosols intended for children have been designed and made available (39). Nasal cannula designs specifically for aerosol delivery to infants have been described and tested using computational fluid dynamics (31). In general, there is a need for the design of aerosol delivery devices specifically for infant and pediatric populations. Such designs would facilitate more efficient delivery of existing therapies and allow for the development of new more dose critical therapies through the inhaled route.

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Footnote

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