



eNeonatal Review

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In this issue... Volume 2, Number 3

Delivery of drugs by aerosol administration offers significant advantages over intravenous or oral drug delivery. By providing direct delivery of the medication to the lungs, the amount of drug needed may be lowered, thereby lowering the cost of treatment while also reducing the risk of systemic side-effects associated with intravenous or oral administration. For these reasons, aerosol medication delivery is now the preferred form of therapy for chronic airway diseases such as asthma and cystic fibrosis, and is being developed as an alternative route of administration for the systemic delivery of peptides such as insulin (1) and for local delivery of vaccines to protect against measles and rubella (2). In addition, inhaled medications are being used with increasing frequency to treat premature infants with chronic lung disease.

The greatest challenge to aerosol therapy in any age group, and in children and neonates in particular, is to deliver an adequate dose of drug to the appropriate lung targets. In studies that quantified the amount of aerosol deposited in the lung via gamma camera imaging (3,4) the amount of drug that actually deposits in the lungs of neonates and children is a) much less than what deposits in the lungs of adults, and b) differs significantly between children.

In this month's issue, we provide an overview of the patient/drug/device-related factors that can lower or improve the aerosol-delivered dose. Our purpose is to assist health professionals who care for neonates and children in choosing devices to optimize pulmonary drug deposition. Factors to be considered are age of the child, the drug to be delivered, and what the child can and is willing to do.

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Reviews by

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COMMENTARY

In babies and young children, delivery of an adequate dose of an aerosolized formulation requires more than simply placing a mask over the baby or toddler's face and turning on a nebulizer, or actuating a metered dose inhaler into a spacer. A number of aerosol-related factors, such as particle size and drug formulation, as well as differences between delivery devices, conspire to reduce delivery to the lungs. Without knowledge of these factors and how they affect delivery, it is likely that dosing will be unreliable and treatment outcome unpredictable. The Rubin article provides an excellent overview of these factors and their relevance to aerosol delivery in infants and young children.

Similarly, a solid understanding of the basics of aerosol science and the various delivery devices is not enough to insure adequate dosing in any age-group. A number of patient-related factors — including the child's anatomy, breathing parameters and cognitive abilities — must also be understood in order to optimize delivery. In addition, the current delivery devices are not intuitive to use, and without adequate training in the proper use of the chosen aerosol-delivery device, patients are likely to derive little benefit from even the best medication formulation. These points

are well-summarized in the article by Everard.

Because of safety concerns, quantification of the dose delivered to the lungs using lung imaging techniques is typically no longer performed in neonates or young children; thus, it is often unknown if an adequate dose of an aerosolized medication has been delivered. To address this problem, aerosol scientists in recent years have begun to design models that can be used to quantify lung dose. These models — often age-specific replicates of a child's face including the nose, mouth and eyes, and/or components of a child's lung — make it possible to estimate the dose delivered to the lung under various breathing conditions such as awake vs. asleep (Janssens et al), or during mechanical vs. manual ventilation with a spacer and metered-dose inhaler (Lugo et al).

Models can also be used to test the effects of changing a drug's formulation and/or some aspect of device design on dose delivered. One major change in aerosol medication formulation that holds promise for improving aerosol delivery to neonates and young children is the replacement of the chlorofluorocarbon propellants (CFCs) used to generate most drugs formulated for metered-dose delivery with hydrofluoralkane (HFA). This propellant is more ozone-friendly and is now replacing CFCs in MDI-propelled albuterol (VentolinTM and ProventilTM) and beclomethasone (QVARTM). Using a model of an infant's face, Janssens et al. describe the differences in lung dosing that result from the two propellant formulations. The therapeutic consequences of these differences in dosing are not yet known, but are likely to be important.

OPTIMUM DELIVERY DEVICES FOR AEROSOLIZED MEDICATIONS IN YOUNG CHILDREN

Rubin BK, Enger M, Fink JB. The delivery of inhaled medication to the young child. *Pediatric Clinics of North America*. 2003;50:717-731.

An overview of the definitions and mechanics of aerosol delivery and the various devices used to generate therapeutic aerosols.

Definitions and Mechanics: Aerosol particle size is defined in terms of mass median aerodynamic diameter (MMAD). The respirable fraction of a therapeutic aerosol is the percentage of particles with MMAD between 0.5 and 5 μ m MMAD. During oral inhalation, particles >5 μ m impact in the oral cavity, or in the device itself, while particles <0.5 μ m are mostly exhaled. Aerosol deposition occurs by three mechanisms: inertial impaction affects particles >3 μ m; gravitational sedimentation affects particles between 1 and 3 μ m; and diffusion affects particles <1 μ m. Inertial impaction increases with high inspiratory flow, such as occurs with a crying infant, and leads to deposition in the extrathoracic airways (i.e. nose and mouth). Gravitational sedimentation increases during a breath hold (4-10 seconds), resulting in enhanced deposition of 1-3 μ m particles in the lung periphery. The low tidal volumes and short respiratory cycles that are seen in infants result in a decrease in gravitational sedimentation. During diffusion, random movement of particles <1 μ m leads to collisions of particles with airway surfaces and subsequent deposition in small airways and the alveolar region.

Aerosol Delivery Devices: Particle size varies significantly between delivery devices. Delivery devices for aerosolized medications include nebulizers, pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs).

For jet nebulizers, aerosol particle size varies with the pressure and flow of compressed air into the nebulizer cup. Compressors that produce flows less than 6 L/min (10-15 psi) are inefficient at generating respirable particles (<5 μ m) and should not be used. All nebulizers have some residual medication remaining in the nebulizer cup at the end of therapy, when aerosol generation becomes intermittent (sputtering). Aerosol delivery declines by half within 20 seconds of sputtering and should be discontinued at this point. Adding saline to the volume of drug in the nebulizer cup will increase the proportion of medication that is nebulized before sputtering occurs. However, this will also prolong the duration of the treatment, which could affect patient compliance. Delivery efficiency is also improved by using breath-enhanced nebulizers and well-fitting face masks. Blow-by administration of nebulizer treatments results in negligible delivery of medication to the child and should not be used.

pMDIs contain a formulation of medication and propellant that is expelled under pressure by

compression of the canister. Drug particles exit the canister coated in propellant, making them large in size and traveling at a high velocity. To minimize extrathoracic deposition due to the large particle size and high velocity, pMDIs should always be interfaced with a spacer. For smaller children, the spacer should be attached to a facemask and medication delivered during tidal breathing. Older patients should use a mouthpiece with a spacer device. A disadvantage of pMDIs is that it is difficult to discern when a pMDI canister is empty. This is because they are loaded with more propellant than drug and will continue to produce noise with each actuation, even though they are no longer delivering medication. Parents need to be aware of how many doses of drug each pMDI will deliver. They should make an attempt to monitor the number of doses used by the child, since there is no dose-counter device associated with pMDIs. Failure to shake the canister before actuation results in drug that is not well-mixed with propellant, so parents should always make sure they shake the canister well. To increase deposition in the lungs, older patients should be instructed to inhale deeply and slowly and hold their breath for at least 4 seconds when using a pMDI with a spacer. For smaller patients who are tidal breathing, the number of breaths that are needed to clear the chamber of medication will vary with the size of the chamber and the child's tidal volume.

A major change in pMDI delivery is that hydrofluoroalkane (HFA) is replacing the traditional chlorofluorocarbon (CFC) as the propellant. This replacement may have a positive impact not only on the environment (CFCs are destroying the ozone layer), but also on aerosol delivery. For example, it has been shown that beclomethasone particles that are generated by an HFA-containing pMDI (QVARTM) have smaller MMADs and lower velocities compared to beclomethasone particles that are CFC-propelled. Since lung deposition of these particles is three-to four-fold higher than CFC-propelled particles, it may be possible to lower the inhaled doses of this medication, while maintaining a good anti-inflammatory outcome.

DPIs can be used by children 5 years old and older with appropriate instruction. With

TurbuhalerTM DPIs, children should inspire as fast as possible (~60 L/min) to empty the dosing chamber. If the patient finds this too difficult, another device should be recommended; for example, the DiskusTM device delivers its medication dose at inspiratory flows as low as 30 L/min.

The authors recommend the use of pMDIs with valved holding chambers, or DPIs as the optimum delivery devices for nearly all infants and children. Physicians and other health care providers need to understand the advantages and disadvantages of each delivery device in order to select an appropriate device for individual patients. Parent and patient education remains key to ensuring that the devices are used appropriately.

Rubin BK, Enger M, Fink JB. The delivery of inhaled medication to the young child. *Pediatric Clinics of North America*. 2003;50:717-731.

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SUCCESSFUL AEROSOL DELIVERY IN INFANTS AND CHILDREN: PATIENT-RELATED FACTORS

Everard, ML. Inhaler Devices in Infants and Children: Challenges and Solutions. *Journal of Aerosol Medicine*. 2004;17:186-195.

A review of the patient-related factors and specific developmental factors that adversely impact aerosol delivery in infants and children.

Two compliance factors impact inhaled therapy in infants and children: regimen compliance (taking a medication regularly) and device compliance (whether or not an inhaler device is used correctly). Available objective data suggests that parents are no more effective at ensuring regimen compliance for their infants and children than they are for ensuring their own compliance. The authors found some limited evidence suggesting that regimen compliance can be improved by using a device that provides feedback related to technique and adherence. Additionally, it may be more important to comply on a regular basis each day than to comply with

the total number of doses prescribed.

In terms of device compliance, devices used to deliver aerosolized medications require significant input and teaching to ensure that they are used effectively. Many patients and/or parents receive very little, if any, instruction when an inhaler or nebulizer is prescribed. With little or no instruction, aerosol delivery devices are often used inconsistently and inappropriately by patients and parents, leading to insufficient delivery of medications to the lungs and rendering the medication partially or completely ineffective.

Anatomical, physiological, cognitive, social, and emotional developmental factors conspire to decrease the lung deposition of aerosolized medications in infants and young children. These patients have smaller airways compared to older children, and they are obligate nose breathers. These anatomical and physiological differences result in increased deposition of aerosolized medication in the extrathoracic airways (i.e. less than 1% of a standard jet nebulizer dose deposited in the lungs of infants). Although smaller doses are delivered to the lungs of infants and young children, when these doses are corrected for weight, they are comparable, if not greater, than those delivered to adults.

Further contributing to extrathoracic deposition in infants and toddlers is the need to use facemasks for delivery (due to limited cognitive development, these patients cannot master the techniques required to use a mouthpiece with an aerosol delivery device). Drug delivery is optimized in these children when they breathe tidally through the facemask while the aerosol is either continuously generated by nebulizer, or after actuation of a pMDI into a reservoir such as a holding chamber. Conversely, drug delivery to the lungs is greatly decreased when the child is crying or screaming because of an inability to achieve an effective facemask seal and because of high inspiratory flow rates. Under these circumstances, choosing a device that is acceptable to the child becomes far more important than choosing a device that is the most efficient in *in vitro* testing. As the child grows and cognitive development expands, the child will gain the ability to use devices with mouthpieces, and choice of device may then be tailored to the child's preferences and skill level.

Despite the many challenges related to the delivery of aerosolized medications to infants and children, these medications can be administered effectively. The key factors to successful delivery are selecting a device that is acceptable to the child (increases regimen compliance) and teaching the patient and/or parent how to use it (increases device compliance).

Everard, ML. Inhaler Devices in Infants and Children: Challenges and Solutions. Journal of Aerosol Medicine. 2004;17:186-195.

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USE OF HFA-PROPELLANT DEVICES & ADMINISTERING MEDICATION DURING SLEEP

Janssens HM, De Jongste JC, Hop WCJ, Tiddens HAWM. Extra-Fine Particles Improve Lung Delivery of Inhaled Steroids in Infants. CHEST. 2003;123:2083-2088.

Janssens HM, Van Der Wiel EC, Verbraak AFM, De Jongste JC, Merkus PJFM, Tiddens HAWM. Aerosol Therapy and the Fighting Toddler: Is Administration During Sleep an Alternative? Journal of Aerosol Medicine. 2003; 16:395-400.

Use of an upper airway model to compare delivered dose using HFA and CFC propellant devices and aerosol delivery via pMDI/spacer during sleep and wakefulness.

Both of these studies used an anatomically correct nose-throat model of a nine-month old infant (SAINT model) attached to a computer-controlled breathing simulator. To simulate obligate nose breathing in infants, the nasal airway in the model was open for air passage, whereas the oral airway was closed. Aerosolized medications were delivered from a pMDI into a spacer with a facemask attached to the model's "face". Therapeutic putty was applied to ensure an adequate

facemask seal. Drug was collected on a filter at a point between the model and the breathing simulator. The amount of drug that was detected on the filter provided an estimate of drug that could be delivered to the lungs.

It is important to remember that these studies were performed in an *in vitro* model and medications were delivered under optimal conditions. In an *in vivo* situation, facemask seal is unlikely to be as secure and breathing patterns are likely to vary.

The first Janssens study investigated HFA-Propellant Devices. Aerosol delivery was measured at tidal volumes (VTs) of 50 mL, 100 mL, and 200 mL with a fixed respiratory rate of 30 breaths per minute. The test drug was beclomethasone dipropionate (BDP) delivered by pMDIs with two different propellants: hydrofluoroalkane-134a (HFA) or chlorofluorocarbon (CFC). Drug was delivered from the pMDIs into an AerochamberTM spacer with an infant facemask, and was drawn from the spacer during 30 seconds of simulated breathing. Drug dose measurements were expressed as a percentage of nominal dose and included total lung dose, fine particle dose (FPD) [defined as the mass of lung dose in particles <4.7µm], and extra-fine particle dose (EFPD) [defined as the mass of lung dose in particles <2.1µm].

Lung doses for HFA-BDP were 25.4%, 26.5%, and 30.7% compared with 6.8%, 4.8%, and 2.1% for CFC-BDP at VTs of 50 mL, 100 mL, and 200 mL, respectively. These differences were significant with $p < 0.001$ for all tested VTs. The lung dose of HFA-BDP did not significantly depend on VT, but lung dose of CFC-BDP decreased significantly with increasing VT. Both FPD and EFPD were also significantly higher for HFA-BDP than for CFC-BDP at all VTs. FPD of HFA-BDP did not significantly depend on tidal volume while FPD of CFC-BDP decreased significantly with increasing tidal volumes. The EFPD for both drugs showed no significant correlation with tidal volume.

The lung dose of approximately 30% reported by Janssens et al. in this *in vitro* study corresponds reasonably well with lung doses observed in an *in vivo* study of children aged 5-7 years old, 8-10 years old and 11-14 years old, who inhaled radiolabeled HFA-BDP (Devadason et al. Eur Respir J 2000;16:Abstract 540S)^{5*}. In that study, the lung dose was 41%, 45% and 54% in the three groups of children, respectively. The lower lung doses observed in Janssens' study are likely due to the use of a spacer and facemask, as well as nose breathing during tidal breathing, versus mouthpiece breathing during inhalation only in Devadason's study. Both mouth-piece breathing and inhalation during inspiration only are known to increase lung deposition, compared to tidal breathing by nose from a spacer.

In general, these results suggest that the delivery of inhaled medications to the lungs of infants may be significantly improved by using an HFA-pMDI with an AerochamberTM spacer versus a CFC-pMDI and the same spacer. However, this finding with BDP needs to be confirmed with other aerosolized drug formulations. Higher lung deposition that is independent of changes in tidal volume may improve delivery of an aerosolized medication to a crying or uncooperative child whose tidal volume may vary significantly throughout aerosol administration. By increasing the lung dose, inhalation of BDP with an HFA-pMDI may also lead to a better long-term treatment outcome in infants compared to CFC-pMDI delivery of BDP.

The second study by Janssens and colleagues compared drug delivery during simulated awake and asleep breathing patterns using the SAINT model. Breathing patterns were recorded from 18 cooperative children with a mean age of 11 (SD 5.1) months, who were referred for lung function tests. The awake-breathing pattern was recorded during tidal breathing with the child seated in an upright position using a pneumotachograph attached to a facemask. Children were then sedated with chloral hydrate and a second breathing pattern was obtained with the child in a supine position while sleeping quietly. These recorded breathing patterns were analyzed for respiratory rate, tidal volume, and peak inspiratory flow, and were then used to drive the SAINT breathing simulator. Mean respiratory rate and peak inspiratory flow were significantly higher for the awake-breathing patterns compared to the asleep-breathing patterns. Once the breathing patterns were established, one puff of budesonide (200 µg) was delivered by a pMDI into a NebuchamberTM spacer with attached facemask. Drug was withdrawn from the spacer through the SAINT model during 30 seconds of tidal breathing that simulated the awake or asleep breathing patterns. The amount of budesonide deposited on a filter located between the model and the breathing simulator (lung dose) was measured immediately after delivery. Lung dose was significantly

higher for the asleep-breathing patterns (11.3 +/- 3.9 µg) compared to the awake-breathing patterns (6.5 +/- 3.5 µg) (p=0.004).

Because the conditions of medication administration were ideal in this study, the results may actually underestimate the true difference between awake and asleep drug delivery. However, it remains unclear whether administration of aerosol to infants during sleep is feasible *in vivo*. For many infants, application of a mask to the face during sleep may result in arousal and crying. Nevertheless, this study provides objective evidence that administration of aerosols during sleep could be an effective alternative to administering aerosol to infants and toddlers who are uncooperative when awake.

Janssens HM, De Jongste JC, Hop WCJ, Tiddens HAWM. Extra-Fine Particles Improve Lung Delivery of Inhaled Steroids in Infants. CHEST. 2003;123:2083-2088.

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DURATION OF VENTILATION FROM AN MDI WITH A SPACER AFFECTS MEDICATION DELIVERY

Lugo RA and Ballard J. Albuterol Delivery From a Metered-Dose Inhaler With Spacer Is Reduced Following Short-Duration Manual Ventilation in a Neonatal Ventilator-Lung Model. Respiratory Care. 2004; 49:1029-1034.

A neonatal ventilator lung model was used to compare albuterol delivered by MDI with a spacer and manual ventilation (5, 15, or 30 breaths) and an in-line spacer with mechanical ventilation for 30 and 60 seconds.

A 2002 survey of 68 academic neonatal institutions found that fifty-seven percent of those institutions used an MDI to administer albuterol to ventilated neonates. Ninety-five percent of the institutions used a spacer with the MDI. The majority of centers commonly used a dose of 2 puffs and waited 30-60 seconds between actuations. Fifty-six percent administered albuterol via manual ventilation following MDI actuation (Ballard J et al. *Resp Care* 2002; 47:31-38)^{6*}. Concern about the dead space added by the spacer has caused some respiratory therapists to limit the amount of time the spacer is in-line in the ventilatory circuit. This study was designed to determine if the duration of a spacer's presence in the ventilation circuit following MDI actuation significantly affected albuterol delivery to an *in vitro* model of a mechanically-ventilated neonatal lung.

The lung model, designed to simulate a 1-kg premature infant with moderate lung disease, consisted of a 1-L cylindrical test lung partially filled with water to create a small tidal volume of 7 mL. The test lung was connected to a 3.0-mm endotracheal tube (ETT), cut to 10 cm and flexed to a 90° curve to simulate placement in a neonatal airway. A VIP Bird ventilator was set to deliver time-cycled, pressure-limited, continuous-flow ventilation with peak inspiratory pressure of 25 cm H₂O, positive end-expiratory pressure of 4 cm H₂O, respiratory rate of 30 breaths/min, inspiratory time of 0.35 seconds, continuous flow of 9 L/min, and fraction of inspired oxygen (FiO₂) 0.40. A filter was placed between the ETT and the test lung to collect aerosolized albuterol delivered to the end of the ETT (lung dose). Albuterol MDI with chlorofluorocarbon propellant was administered using 5 different methods.

The first three delivery methods used the cone-shaped ACETM spacer placed horizontally between the ETT and a bag-valve-mask. The MDI was actuated immediately prior to an inspiratory

breath and was followed by 5, 15, or 30 manual breaths after each actuation (with flow 6 L/min, rate 30 breaths/min, and peak inspiratory pressure 25 cm H₂O). All manual ventilations were performed by one investigator. The final two delivery methods used an in-line ACETM spacer placed horizontally between the circuit Y-piece and the ETT, with the spacer kept in line for 30 seconds or for 60 seconds after each actuation. Each experiment was conducted by actuating 10 different albuterol canisters twice for a total delivered dose of 2000 µg to ensure that the amount of drug that was collected on the filter was above the limit of detection for the albuterol assay. Results were reported as percent of albuterol delivered.

Percent of drug delivered was 2.3 +/- 0.5, 3.6 +/- 1.8, and 5.1 +/- 1.3 for 5, 15, and 30 manual breaths, respectively. Percent drug delivered was 3.7 +/- 1.3 and 3.7 +/- 0.6 for in-line spacer placement of 30 seconds and 60 seconds, respectively. These data indicate that the duration of ventilation after administration of albuterol from an MDI with a spacer significantly affects medication delivery. Delivery was significantly reduced by removing the spacer from the ETT after 5 or 15 manual breaths (10 or 30 seconds, respectively), compared to 30 manual breaths (60 seconds) (p<0.05). In addition, albuterol delivery was greater when the spacer remained in line for 30-60 seconds after each actuation, compared to removing the spacer after 5 manual breaths per actuation. Although this study did not address the risk of hypercarbia from having the spacer in line for a prolonged time period, other *in vitro* studies have suggested that keeping the ACETM spacer in line for several minutes does not increase the risk of hypercarbia in mechanically ventilated premature neonates.

These results also illustrate the importance of standardizing the method of administration of albuterol via MDI to mechanically ventilated infants within a facility. Without such standardization, there is likely to be significant variability in dosing, potentially leading to adverse effects and incorrect conclusions regarding dosage requirements for individual patients. Establishing a uniform method of administration of albuterol via MDI to intubated neonates would help to ensure consistent drug delivery and aid clinicians in drawing conclusions regarding the response of individual infants to aerosolized bronchodilator therapy.

A final note: the reader is reminded that this *in vitro* study applies specifically to the conditions described and should not be extrapolated to a broader neonatal population in which respiratory rates, tidal volumes, and other variables will likely differ from those described in this study.

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Learning Objectives [back to top](#)

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CE activity. At the conclusion of this activity, participants should be able to:

- Develop a better understanding of the advantages offered by aerosol delivery of drugs to neonates and children;
- Understand the factors that must be taken into account to make aerosol dosing reliable and outcomes predictable;
- Appreciate the need to establish standardized protocols based on the specific drugs/devices/patients.

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- Dr. Nogee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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