Special Problems in Aerosol Delivery: Neonatal and Pediatric Considerations

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Introduction

The importance of aerosol therapy in the management of respiratory disorders of pediatric patients has continued to increase over the past 15 years. This is due not only to an apparent increase in the occurrence of reactive airway disorders and greater utilization of aerosol therapy among pediatric patients with reactive airway disease,[1] but also to expanded applications for other clinical disorders, such as cystic fibrosis,[2] intervention for infectious processes,[3] and neonatal chronic lung disease (or bronchopulmonary dysplasia).[4–6] The breadth of clinical indications reflects the broader spectrum of pediatric patients utilizing aerosol therapy. Therefore, pediatric aerosol utilization encompasses patients as small as premature infants born at 24 weeks gestation (< 750 g birth weight) to adult-size teenagers. This diverse population, particularly premature neonates through young children, presents major challenges to effective, efficient aerosol therapy.[7–10] In addition to therapeutic incentives to deliver more effective therapy, there are economic and safety incentives, particularly for medications with lower safety profiles and higher cost.

The rationale and theoretical advantages of aerosol therapy are the same for pediatric patients as for adults: (1) to administer a lower dose of the medication, relative to that required for systemic therapy (in order to achieve a therapeutic effect with fewer systemic adverse effects) (2) direct delivery of the drug to the target organ, and (3) more rapid onset of action.[8,9] The goals of aerosol therapy include optimizing lung function and avoiding further lung damage.[10] These goals require careful, ongoing consideration of optimizing the benefit of the pulmonary status versus the acceptability of risks, especially in patients treated with inhaled steroid therapy.

The therapeutic efficacy of aerosolized medication for treating respiratory disorders depends upon delivery of adequate dose to the targeted sites within the lung. The primary factors influencing lung deposition include (1) aerosol particle size and the amount of respirable aerosol delivered, (2) the patient's breathing pattern and underlying disorder, (3) the aerosol delivery system and use of the delivery system.[8–10] Information regarding inhaled mass, lung deposition, and regional distribution of aerosolized medication is limited in neonates and young children. Data from in vitro models, animal studies, and in vivo infant studies indicate that aerosol delivery efficiency is lower and variability higher in infants and young children than in adults.[11–21] Aerosol delivery to a spontaneously-breathing adult with good inhalation technique is estimated to range from 10–25% of the nominal aerosol dose,[18] in contrast to 5–10% for a ventilated adult[19] and < 5% for a ventilated or spontaneously-breathing infant.[20] Fok et al found in vivo < 2% aerosol deposition by metered-dose inhaler

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(MDI) with spacer and jet nebulizer in spontaneously-breathing and ventilated infants with bronchopulmonary dysplasia.[21] Therefore, the precision, efficiency, and reproducibility of aerosol delivery to infants and children are limited by anatomical and physiologic factors, efficiency and use of aerosol delivery systems, and characteristics of the aerosol output.[8–10,20] Compensating for this inefficiency is often accomplished by increasing the nominal dose delivered in order to achieve a clinical effect. Therefore, special considerations relevant to infants and young children are required to optimize both aerosol delivery efficiency and therapeutic effect, and to minimize drug waste and adverse effects. This article reviews issues related to the infant and young pediatric patient.

Patient Considerations

Age-related patient considerations include anatomical, physiologic, and pathophysiologic considerations, as well as patient capability, cooperation, and compliance.[8–10,22] With respect to anatomical considerations, nasal breathing results in unpredictable loss of drug particles > 2 μm in diameter.[8] Therefore, the variable impact of nasal breathing must be considered among infants who are obligate nasal breathers and young children wearing face masks.[8–10,23] The smaller oropharynx reduces the amount of aerosol reaching the lower airways, as demonstrated in an in vitro comparison of replicas of an adult-size oropharynx and a child-size oropharynx, in which 35% of the nominal dose traversed the adult-size oropharynx, compared to 15% via the child-size oropharynx.[24] The mean airway lumen diameter from the main bronchi to respiratory bronchioli increases by 200–300% between birth and adulthood.[25] The smaller airway caliber of infants and children needs to be considered, since it may reduce aerosol delivery to the peripheral airways by favoring a more central pattern of deposition.[8,9,21] The small airway caliber can be further compromised by inflammation, edema, mucus, bronchoconstriction, and distorted airway growth and remodeling.[9] Aerosols with a greater proportion of fine particle fraction (< 3 μm) may negotiate the lower airways more effectively than aerosols with larger respirable size distribution. It is also important to be aware of the fact that postnatal alveolar development continues after birth through at least 2 years of age, with a disproportionate growth in lung volume relative to airways. The number of alveoli present at birth is estimated to be $20–150 \times 10^6$, compared to $300–600 \times 10^6$ in the adult. After alveolar development is complete, the alveoli continue to increase in size.[26] The normal growth and development of alveoli and airways after premature birth is often disrupted by assisted ventilation and neonatal chronic lung disease and its attendant fibrosis and remodeling. Therefore, acute and chronic lung disease may significantly affect the amount and pattern of aerosol deposition due to altered airway flow and atelectasis. In addition, postnatal systemic steroid therapy may contribute to abnormal pulmonary growth and development.[27] It is important to be aware of the ongoing pulmonary development so that adequate emphasis is given to achieving optimal therapeutic effect as early as possible in order to facilitate normal lung growth and development and to evaluate the effect of inhaled steroid therapy on developing lung. Inadequate therapy may result in life-long compromise in pulmonary development and function.

Two other major patient-related considerations include the highly variable breathing patterns and pulmonary mechanics of infants and children.[8–10,22] These physiologic considerations are among the primary determinants of aerosol deposition, and are greatly influenced by cooperation and underlying pathophysiology. The highly variable inspiratory flows are problematic for children of any age, but especially among crying infants, as it may result in decreased delivery to the lungs. The impact of variable inspiratory flow on the amount of respirable particle deposited in the lung depends on the extent of how high or low the flow, and also varies by aerosol device. For example, slower inspiratory flow is better for MDI, but maximum inspiratory flow is necessary for optimal dry powdered inhaler (DPI) performance in children capable of generating sufficient inspiratory flow. Among infants, the lower tidal volume (V_T), lower inspiratory flow, increased respiratory rate, and shorter breath-holding time decrease the dose delivered to the lungs.[8–10] A slower respiratory rate and appropriate inspiratory flow can improve aerosol deposition. Although low V_T is associated with lower dose delivery, and large, deep inspiratory volumes enhance deposition, recent evidence suggests that tidal breathing may result in similar benefit to slow, deep breaths with breath-holding.[28,29] Breath-holding appears to benefit deposition with MDIs and dosimetric nebulizers.[8] In addition to a patient's respiratory pattern, aerosol deposition is clearly affected by the type and severity of the underlying disease process with its attendant abnormal lung function and airway remodeling. Deposition may be heterogeneous and/or more central as obstructive airway disease progresses.[8–10,21,30]

Other patient-related considerations include a child's capability, compliance, and acceptance of aerosol therapy.[8–10,22] A child's capability to optimally utilize various aerosol generators and devices changes as he or she matures. Compliance and acceptance of aerosol delivery systems are additional challenges for young children because aerosol therapy requires preparation and maintenance, appropriate time to administer, cooperation, and correct technique by the operator and the child. These considerations are discussed further under selection of delivery system.

Aerosol-System Considerations

Aerosol-system considerations relate to factors that influence the amount of aerosol output and the characteristics of the aerosol output, such as particle size distribution. These "system" factors include medication formulation and concentration, the specific aerosol generator and aerosol delivery device, the interface between device and patient (ie, face mask, mouthpiece, or endotracheal tube), the operating conditions (eg, the driving gas flow), and the technique utilized by the operator and/or patient.[8–10,31]

Considerations regarding optimal aerosol particle size are similar for pediatric and adult patients in that it is preferable to have an aerosol particle size distribution that deposits in the lower respiratory tract. The optimal aerosol particle size is not known with certainty for infants and children. The range of 1–5 μm is often considered the range that has the greatest likelihood of depositing in small conducting airways and alveoli. It has been suggested that aerosol particles of 1–2 μm may provide the greatest lung dose to negotiate the small airways of infants. Finer particle size (< 3 μm) may be beneficial in nasal breathers and in children with obstructive airway disease. Therefore, it is important to consider the medication formulation and the aerosol system that will provide a greater fraction of particles within the desired aerosol particle size range.[8–10,31] Hydrofluoroalkane (HFA) reformulations of medications may favorably influence the aerosol particle size distribution, such as the HFA reformulation of beclomethasone.[32] However, many medications have not yet been reformulated with HFA propellants. Each reformulation will require evaluation regarding the effect of reformulation on aerosol particle behavior and size distribution.[33]

The available methods to aerosolize medications are nebulization (jet or ultrasonic), MDI, and breath-actuated DPI.[8,10,31] Numerous designs of each method are available, along with an increasing number of devices to facilitate aerosol delivery. Nebulization and pressurized MDIs with spacers are the two most effective options for infants and young children. DPI is a convenient aerosol method that uses micronized particles and contains no FREON propellant. However, since the efficiency and aerosol particle size of DPIs depend on rapid inspiration, their utilization has been limited to older children ($> 4-6$ years old) who are capable of generating sufficiently rapid inspiratory flow ($\geq 30-120$ L/min). New designs of DPIs with power-assisted flow that is independent of inspiratory flow may increase the number of children who can effectively utilize this method.[10,31,34–36]

Nebulization, by jet or ultrasonic nebulization, has been and continues to be a popular method to administer aerosol medications to infants and young children, despite the numerous factors that affect nebulized aerosol output and particle size.[7–11,14,15,31,37] Because of inefficient, highly variable output and poor reproducibility in aerosol particle size among different nebulizing devices, and even among devices of the same model, use of jet nebulization has shifted toward other alternatives, such as MDI with spacer, for infants and young children, and MDI with spacer or DPI for older children. The advantages of nebulization are that it can be used by patients of all ages and that it requires tidal breathing. It can also be administered intermittently or continuously over several hours, such as with high doses of β agonists delivered for prolonged periods.[38] Also, certain drugs can only be nebulized, such as antibiotics, surfactants, rhDNAse, and pentamidine. Advances in jet nebulizer technology may reduce their inefficiency and variability, improve the aerosol particle size, reduce medication waste, and reduce leakage of medication to the environment.[8–10,31] These modifications include improved designs, with breath-actuation dosimetry, entrainment of air via the nebulizing chamber, improved valves, and new plastics and molding techniques. Ultrasonic nebulization may have a higher aerosol output, slightly larger particle size distribution, and may minimize wastage of drug, compared to jet nebulization. Ultrasonic nebulization is not suitable for suspensions or viscous medications (such as antibiotics). Increased temperature of the fluid in ultrasonic nebulizers may denature protein solutions. A disadvantage of ultrasonic nebulization is that the equipment is expensive. Similar to jet nebulization, ultrasonic nebulization requires relatively more processing and maintenance than MDI with spacer or DPI, but if portability and performance are improved and if costs are contained, ultrasonic nebulizers may see increased use. Consideration of the patient interface with nebulization is important. Mouthpiece devices improve aerosol delivery by bypassing nasal filtration, but infants and young children may require a face mask during nebulization treatments. Close-fitting face masks with low-resistance exhalation valves and minimal dead space enhance aerosol delivery.[8–10,31]

MDIs dispense metered doses of micronized medication suspended in propellants along with surfactants. Use of the MDI alone is not appropriate for infants or young children because of the requirement to synchronize aerosol actuation with inhalation. Combining the MDI with a spacer or holding chamber lessens problems of coordinating actuation and inhalation, and decreases deposition of medication in the oropharynx due to reduction in aerosol velocity, inertial impaction, and selective removal of nonrespirable particles. The net effect is that aerosol output is increased, with improved delivery of respirable-size particles to smaller airways.[8–10,31]

MDI/spacer systems can be utilized for spontaneously-breathing infants with attached face mask, or with ventilated infants with the spacer connected in-line with the

ventilator circuit or directly attached to the endotracheal tube. The choice of spacer is an important consideration for infants and children, specifically with respect to the design, presence of low-resistance valves or no valves, volume, and electrostatic charge.[8–11,31,39–43] All the factors are critically important, since aerosol delivery efficiency varies among spacers, ventilatory variables, and conditions of use.[8–11,31]

There are 3 basic types of spacer: the open tube design, the reverse-flow design, and the holding chamber.[8–11,31,39–43] The two nonvalved spacers (open tube and reverse-flow) require some synchronization of inhalation with ventilation to minimize loss of aerosol.[8–10,31,42] Inhalation valves of spacers for infants or young children must have sufficiently low resistance to open readily with low inspiratory flow.[11,39,42] Although a one-way, low-resistance, valved holding chamber reduces loss of aerosol and allows the aerosol to be contained for a finite period of time until the child inhales, Fok et al recently found that nonvalved spacers are more effective than low-resistance valved spacers for aerosol delivery in spontaneously-breathing newborns and small infants.[40] These findings suggest that an MDI/spacer system with no low-resistance valve may actually deliver more aerosol to spontaneously-breathing infants. Further evaluation is needed of the benefit of low-resistance valves versus no valves in the context of ventilated or spontaneously-breathing neonatal/infant aerosol therapy.

The size of the spacer is important relative to aerosol concentration, particle impaction, and V_T.[8–11,31,41] Smaller-volume spacers result in greater aerosol concentration and particle impaction than larger volume spacers. The volume of the spacer should be appropriately low to facilitate the maximum amount of drug inhalation with a few inhalations for infants and children with low V_T ($<$ 50 mL).[9,11,31,42]

Electrostatically charged plastic holding chambers reduce the total and respirable-size particle output because of the attraction of the electrostatically charged aerosol particles to the walls of the holding chamber.[44] The electrostatic charge of a holding chamber can be reduced by proper cleaning with a mild detergent, air drying, and priming the spacer with a thin surface of the aerosol prior to using the spacer. O'Callaghan et al demonstrated that application of an antistatic lining to the holding chamber increased total aerosolized cromolyn output five-fold and respirable-size particles two-fold, compared to the holding chamber without the antistatic lining.[44] The development of a nonelectrostatic holding chamber improved aerosol output by increasing the residence time of respirable-size particles and the availability of aerosol particles for inhalation.[45]

Incorrect and inconsistent use of an MDI/spacer system because of lack of understanding of factors that affect aerosol delivery or inattention to operating conditions can cause ineffectiveness, inefficiency, and greater variability in the dose delivery beyond the inherent differences in the MDI/spacer systems per se. Shaking the MDI suspension, priming the MDI metering valve with a few actuations before administering treatment, and avoiding rapid, multiple actuations are a few easy-to-control factors that can improve aerosol delivery for infants and young children. Immediate inhalation following actuation is important for optimizing aerosol delivery, but is not easy to control for spontaneously-breathing infants and children.[44,46] For ventilated infants and children, immediate manual or mechanical inhalation after actuation, along with attention to ventilatory variables (flow, V_T, inspiratory time), improve aerosol delivery and decrease variability.

The type of patient interface (eg, endotracheal tube, face mask, or mouthpiece) requires consideration.[11,31] Endotracheal tubes are choke points for reducing aerosol delivery.[47] Attention to endotracheal tube adapter design and aerosol particle size may lessen the impact of the endotracheal tube adapter. For young patients not capable of using mouthpieces, the face mask should be close-fitting, have minimal dead space, no holes for air entrainment, and low-resistance exhalation valves to enhance available aerosol without dilution and to minimize loss of aerosol.

Just as the breathing patterns and pulmonary mechanics of spontaneously-breathing infants and young children are important, close attention to operating conditions and ventilatory variables to ventilated patients is important. These considerations include attention to the placement of the MDI/spacer (in-line with ventilator circuit or attached to the endotracheal tube adapter), gas flow, V_T, peak and end-expiratory pressures, respiratory frequency, inspiratory time, and synchronization of actuation with inspiration.[8]

The MDI/spacer combination is convenient and can be utilized by patients of all ages, including ventilated and spontaneously-breathing premature infants. Treatment time with MDI/chamber combination is less than that with nebulization. Many MDI medications that are currently suspended in chlorofluorocarbon propellants are being reformulated to HFA propellants. Reformulation may alter the aerosol output and particle size for different medications. Knowledge of the aerosol output and particle size distribution of the specific medication and aerosol MDI/spacer system being utilized, and knowledge of the conditions under which the medication and system are tested are both necessary to make decisions regarding dosing and in assessing response.[32,33]

Choosing an Aerosol Delivery System

The choice of an aerosol delivery system for an infant or child is influenced by multiple factors, including the aero-

sol options that are available and feasible given the medication prescribed, the patient's capability of effectively utilizing the device, and what is affordable or reimbursable. Consideration of the drug to be aerosolized and the patient's age and capability are obvious starting points for choosing an aerosol delivery system. Premature and full-term newborns, infants, and children $> 4-6$ years of age can utilize MDI/spacer systems and nebulizers. Holding chambers that are approximately 150 mL appear to benefit infants with low V_T (< 50 mL). The low-resistance-valve holding chamber is currently the better option for delivery of inhaled steroids to infants and young children. Use of new hydrofluoroalkane-propelled MDI products (such as salbutamol and beclomethasone) may provide better aerosol particle size for deposition to the peripheral airways.[33] For children $> 4-6$ years old, MDI/spacer, nebulizer, and DPI are aerosol system options. Newer developments of DPIs with automatic-spacer devices, such as one developed with a breath-independent, mechanical actuation and a noneletrostatic spacer, may provide DPI aerosol options to younger children, since the new design requires no active cooperation and provides pure drug.[34]

Summary: Considerations for Improving Aerosol Delivery to Infants and Children

Identification of the determinants of efficient aerosol delivery and the specific challenges of aerosol delivery to infants and children can facilitate a systematic approach to optimize aerosol delivery to this population. There are inherent anatomical, physiologic, pathophysiologic, and technical limitations of aerosol efficiency in infants and young children. Nevertheless, one can enhance aerosol efficiency through application of sound principles of aerosol delivery and by exerting control over factors that are amenable to intervention. Improvements in aerosol formulations and delivery systems are being made that will enhance efficiency, decrease risk, and reduce waste and cost. Attention to aerosol particle size (1–3 μm mass median aerodynamic diameter and geometric standard deviation < 2 μm), and the concentration of this respirable particle fraction produced by an aerosol system may enhance delivery through endotracheal tubes and to the lower respiratory tract in infants and children with low V_T and low inspiratory rates. Attention to the choice of delivery system and to details of proper MDI technique (shaking, priming, immediate actuation, and avoiding multiple actuations prior to inhalation), choice of the aerosol spacer and patient interface (type of face mask, endotracheal tube, mouthpiece), spacer cleaning, and consideration of the medicine to be aerosolized (solution or suspension, viscosity) permit adjustment of the aerosol regimen to optimize delivery. All the patient-related, system-related, and operator-dependent considerations combined can greatly impact aerosol delivery efficacy and improve therapeutic response. Therefore, education and motivation of medical personnel, parents and caregivers, and patients regarding factors that influence aerosol efficiency and teaching of proper technique must be prioritized in order to improve aerosol delivery.

Aerosol therapy to all patients, especially infants and young children, would be well served if we had a clear understanding of the efficiency and functional differences among the various drugs and devices. These are substantive issues with daily therapeutic impact that have received increasingly outspoken concern over the past decade by aerosol scientists and clinicians.[7–10,22,31,33,48,49] These issues must be given due attention by drug and device manufacturers as well as by regulatory agencies. The medication, the device, and the conditions under which they are tested must be considered together and studied as thoroughly as the medications themselves with respect to total output and particle size distribution. As noted by Bisgaard,[10] medication dose recommendations are useless unless the device and technique used are specified. Medication dose recommendation could be facilitated by setting equivalent standards for generic and brand-name medications and devices. In addition, standardization of in vitro models with better replicas of infants' and children's anatomy (oropharynx, upper airways), and better in vitro lung models, plus utilization of realistic breathing patterns of infants and children will improve in vitro prediction of the in vivo dose delivered to lower airways. This would greatly facilitate selection of delivery systems under specific circumstances for infants and children of various ages.[9,10,31] Safety profile, therapeutic efficacy, and efficiency of aerosolized medications delivered to infants and children need to be rigorously studied. This is particularly true for medications with potentially great benefit but possible adverse effects, such as inhaled glucocorticoid therapy in extremely premature infants. Common sense, ethics, and due respect for the same high standard of approval requirements of adults and older children should motivate further research in understanding and improving aerosol delivery in infants and young children.

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