

Aerosol Delivery to Ventilated Infant and Pediatric Patients

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Summary

Infants have low tidal volume, vital capacity, and functional residual capacity, and short respiratory cycles (low I:E ratio), which result in a low residence time for aerosol particles and, thus, low pulmonary deposition of aerosol particles (< 1% of the nominal dose), compared to adults (8–22%). Scintigraphy data suggest aerosol deposition of < 1% in both intubated and nonintubated infants. In vitro testing appears to overestimate pulmonary deposition, partly because in vitro testing does not account for exhaled aerosol. Animal models of infant ventilation tend to agree with data from human studies. However, though only a small percentage of the aerosol deposits in the lung, infants nevertheless receive considerably more aerosolized drug per kilogram of body weight than do adults. Efficient aerosol delivery to infants is challenging because of low deposition and high inter-patient and intra-patient variability, but existing systems can effectively delivery various aerosolized drugs, including bronchodilators, anti-inflammatories, and anti-infectives. Use of a nebulizer that has a low residual volume (of drug remaining in the device after nebulization) delivers up to 13%. Awareness of the variables that impact aerosol delivery efficiency can result in more effective treatment of mechanically ventilated infants. *Key words: aerosol, neonatal, pediatric, nebulizer, metered-dose inhaler.* [Respir Care 2004;49(6):653–665. © 2004 Daedalus Enterprises]

Introduction

On the surface, aerosol delivery to mechanically ventilated infants presents a relatively simple proposition:

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James B Fink MSc RRT FAARC presented a version of this report at the 49th International Respiratory Congress, held December 8–11, 2003, in Las Vegas, Nevada.

smaller patients receive less aerosol than larger pediatric patients or adults, with a lower percent of the initial dose reaching the infants' lungs. In fact, the delivery efficiency of nebulizer aerosol is so poor and the inconvenience of integrating nebulizers into the ventilator circuit so great that many clinicians avoid delivering aerosols to infants

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through the ventilator circuit. However, as we delve a bit deeper into the observations of researchers over the last 2 decades, it becomes evident that, pound for pound, infants receive considerably more drug per kilogram of body weight from aerosols than do adults. In this review I discuss the basis of aerosol delivery during infant ventilation and methods and technology to optimize the efficiency of aerosol delivery to infants.

How Are Infants Different?

The fetus has a fully defined conducting airway early in its development, but the size of the airways change dramatically in the first years of life. Breathing patterns, flows, and volumes all change with growth and development. Resting respiratory rate decreases with age as tidal volume (V_T) and minute ventilation increase. In the first year of life V_T is approximately 7 mL/kg and V_T increases about 300% in the first year. Inspiratory flow also increases with vital capacity. Because infants have low V_T , low vital capacity, low functional residual capacity, and short respiratory cycle, aerosol particles have a short residence-time in the airways, which hampers pulmonary deposition.

We have only limited data regarding inhaled particle mass, lung deposition, and regional distribution of aerosol in neonates, infants, and young children. This dearth of data is due in part to ethical issues about in vivo measurement of deposition in children, such as concerns about the use of radiolabeled aerosols. The existing data suggest that aerosol delivery is substantially less efficient in that population. Pulmonary deposition of nebulizer aerosol in neonates may be < 1% of the nominal dose, compared to 8–22% in adults.¹ However, that low deposition efficiency may result in infants receiving weight-appropriate doses. For example, deposition efficiency of 0.5% of a standard dose of albuterol sulfate (2,500 μg) would result in a lung dose of 12.5 μg (6.25 $\mu\text{g}/\text{kg}$ for a 2-kg infant), whereas a 70-kg adult with 10% deposition would receive a lung dose of 250 μg (3.6 $\mu\text{g}/\text{kg}$). That is, the low efficiency of deposition in infants compensates for the fact that a standard adult dose would be too large. To some extent the low deposition in infants and children provides a comparable safety and efficacy profile to that of adults. Consequently, rationales to reduce doses for infants and small children have not been well substantiated in the literature.

Factors That Affect Aerosol Delivery and Lung Deposition

Figure 1 illustrates the bench-study data on the relationship between patient age, breathing pattern, nebulizer output, and drug inhaled, with the Pari LC Star nebulizer.² The nebulizer output is about the same with the infant, child, and adult breathing patterns, but infants and small

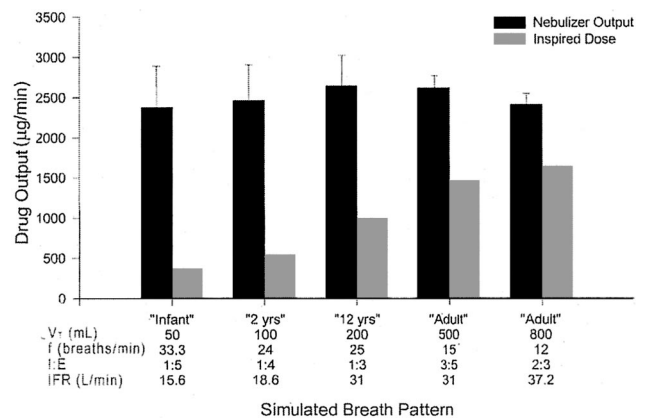


Fig. 1. In vitro measurement of cromolyn sodium aerosolized by a Pari LC Star nebulizer, with infant, child, and adult breathing patterns. The amount of drug delivered to the filter per minute of nebulization increases with tidal volume (V_T), inspiratory flow, and inspiratory-expiratory ratio (I:E), and deposition approaches the nebulizer's per-minute output when it is driven continuously. f = respiratory rate. IFR = inspiratory flow rate. (From Reference 2, with permission).

children inhale a smaller percentage of the emitted aerosol than do larger patients (ie, the drug captured by the filter at the mouth of the in vitro model differs among the simulated breathing patterns). V_T , inspiratory-expiratory ratio (I:E), and inspiratory flow are key to efficiently inhaling nebulizer aerosol. In infants < 6 months old, low inspiratory flow and low I:E (eg, 1:5) result in less aerosol being inhaled (than with a larger child or adult) (Fig. 2).¹

Table 1 lists factors that can limit aerosol penetration and deposition in neonates and infants, to as little as 0.1–1% of a nebulizer or metered-dose inhaler (MDI) dose, regardless of whether the patient is breathing spontaneously or intubated. To address this issue we begin with deposition studies of nonintubated, spontaneously breathing infants and children.

Aerosol Administration in Nonintubated Infants and Children

Only a few studies have measured aerosol deposition in nonintubated infants and children (Table 2).

Using sodium cromoglycate as a nontoxic marker, Salmon et al assessed aerosol delivery (to 9 wheezy infants) from a metered-dose inhaler (with spacer) via face mask versus and from a nebulizer via face mask.³ The concentration of sodium cromoglycate was estimated via timed urine collections to find out how much of the dose was absorbed from the lung. Only 0.13–0.61% of the 20-mg nominal dose was detected in the urine, representing an estimated 0.3–1.5% deposited in the lung.

Chua et al⁴ studied 12 sleeping infants (median age 0.8 y) and 8 older children (median age 10.8 y) with cystic

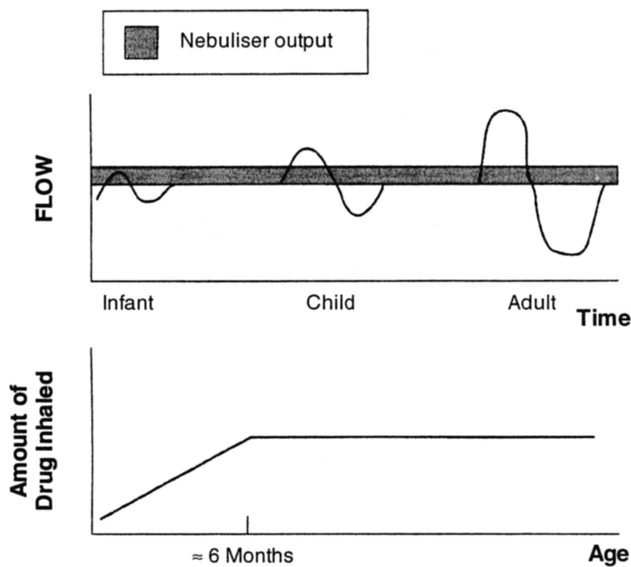


Fig. 2. Upper panel: Respiratory flow patterns of infants, children, and adults, and output of a continuous jet nebulizer. Lower panel: Relationship of patient age to amount of drug inhaled. The differences in airway anatomy and respiratory pattern substantially hamper aerosol delivery in infants < 6 mo old. (From Reference 1, with permission).

fibrosis. Radiolabeled normal saline was placed in a Turret nebulizer with driving flow of 9 L/min. In the infants the median lung deposition was 1.3% (range 0.3–1.6%) and in the older children it was 2.7% (range 1.6–4.4%).

Mallol et al⁵ studied 20 asymptomatic infants with cystic fibrosis to determine the deposition of radiolabeled aerosol (normal saline plus 4 millicuries of technetium^{99m} bound to diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA)). Using a nebulizer that produced an aerosol with particles of mass median diameter 7.7 μm, deposition in sedated infants (0.97 ± 0.35%) trended higher than in nonsedated infants (0.76 ± 0.36%). The best deposition (2.0 ± 0.71%) was reported in the nonsedated infants who inhaled an aerosol that had particles of mass median diameter 3.6 μm.

Amirav et al⁶ evaluated the lower-respiratory-tract distribution of nebulized bronchodilators in infants suffering acute bronchiolitis. Twelve infants (8 mo ± 4 mo) admitted for acute respiratory syncytial virus bronchiolitis were treated with ^{99m}Tc-labeled albuterol aerosol. Gamma scintigraphy was used to assess total body deposition, lung deposition, and pulmonary distribution. Over 6 min, 1.5% ± 0.7% of the nebulized dose reached the right lung, and one third of that amount (0.6%) penetrated to the peripheral lung. There was 7.8% ± 4.9% deposition in the upper respiratory and gastrointestinal tracts, and 10–12% adhered to the patient's face. No correlation was found between any of the deposition indices and clinical response.

Table 1. Factors That Could Affect Aerosol Delivery and Deposition in Infants

Ventilation variables
Pressure-limited vs volume-limited
Continuous flow of gas through circuit
Respiratory rate
Tidal volume
Inspiratory flow rate
Inspiratory-expiratory ratio
Circuit characteristics
Diameter
Length
Adapters
Endotracheal tube
Size
Type
Nebulizer
Fill volume
Particle size
Aerosol output rate
Gas flow rate
Continuous or intermittent nebulization
Metered-dose inhaler
Adapter/spacer
Timing of actuation
Position of the aerosol device in the ventilator circuit
Humidification
Density of gas
Drug formulation

In a later study Amirav et al⁷ compared lung deposition with a tight-fitting small-volume nebulizer aerosol mask and a prototype hood attached to a small-volume nebulizer. Radiolabeled albuterol was administered at random via small-volume nebulizer plus either mask or hood to 14 wheezy infants (mean age 8 ± 5 mo). Mean total lung deposition was 2.6% with the hood and 2.4% with the mask (Fig. 3).

Tal et al⁸ studied 15 children (mean age 21 mo, age range 3 mo to 5 y, mean weight 9.3 kg, weight range 3.2–15 kg). Each patient was imaged with a gamma camera immediately after 1 puff of radiolabeled albuterol administered via spacer with mask. Mean aerosol deposition was 1.97% ± 1.4% in the lungs, 1.28% ± 0.77% in the oropharynx, and 1.11% ± 2.4% in the stomach.

Wildhaber et al⁹ studied children (2–9 y old) who had stable asthma. The subjects inhaled radiolabeled albuterol from a nebulizer and from an MDI, through a nonstatic holding chamber. With the nebulized aerosol the mean lung deposition was 5.4% of the nebulized dose (108 μg) in children < 4 years old and 11.1% of the nebulized dose (222 μg) in children > 4 years old (Fig. 4). With the MDI aerosol the mean lung deposition was 5.4% of the dose (21.6 μg) in children < 4 years old and 9.6% of the dose

Table 2. Aerosol Deposition Studies With Nonintubated Children

Researchers	No. of Patients	Type of Patients	Aerosol Device	Deposition (%)
Salmon et al ³	9	Infants	Nebulizer vs MDI with spacer	0.3–1.5
Chua et al ⁴	12	Infants (≤ 8 mo)	Nebulizer	0.3–1.6
Chua et al ⁴	8	Children (≤ 10 y)	Nebulizer	1.6–4.4
Mallol et al ⁵	20	Infants	Nebulizer	0.76–2.0
Amirov et al ^{6,7}	26	Infants	Nebulizer	1.5–2.6
Tal et al ⁸	15	Children (≤ 21 mo)	MDI with spacer	1.97
Wildhaber et al ⁹	17	Children (2–9 y)	Nebulizer vs MDI with spacer	5.4–11.1

MDI = metered-dose inhaler.

(38.4 μg) in children > 4 years old. The percentage lung deposition of radiolabeled albuterol was equivalent with the nebulizer and the MDI-with-holding-chamber for the 2 groups. However, the delivery rate per minute and the total dose of albuterol deposited were significantly higher with the nebulizer.

Aerosol Deposition in Intubated Infants

Fok et al¹⁰ measured radiolabeled albuterol deposition with jet nebulizers and MDIs in ventilated and nonventilated infants suffering bronchopulmonary dysplasia. In a randomized, crossover sequence they administered 2 MDI puffs (200 μg) or jet-nebulized the albuterol (100 μg/kg at 5 L/min for 5 min) to 10 ventilated and 13 nonventilated premature infants (mean birthweight 1.1 kg). The nonventilated infants inhaled aerosol through a face mask connected to an MDI with spacer. Their lung deposition was 0.67 ± 0.17% of the dose. With the nebulizer with face

mask the lung deposition was 1.74 ± 0.21% of the nebulized dose and 0.28 ± 0.04% of the total initial reservoir dose (Fig. 5A). The ventilated group received mechanical ventilation from a Sechrist Model IV-100B ventilator and the circuit was heated and humidified. An MDI chamber was inserted between the Y-piece and the endotracheal tube (ETT). Lung deposition was 0.98 ± 0.19% of the MDI dose. The nebulizer was inserted in the inspiratory limb, 20 cm from the Y-piece. Lung deposition was 0.95 ± 0.23% of the nebulized aerosol (0.22 ± 0.08% of the total initial reservoir dose) (see Fig. 5B). In both groups and with both delivery methods the aerosol was evenly distributed between the right and left lungs, there was marked intersubject variability in lung deposition, and there was a tendency for the aerosol to be distributed to the central lung regions. The percentage of the dose deposited was low for all delivery systems, with considerable variability among the patients. Lung deposition in the ventilated infants was very similar to that found in previous in vitro, in vivo animal, and indirect human studies.

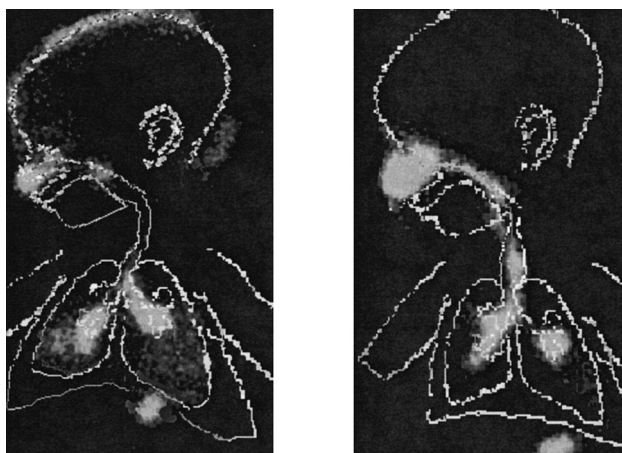


Fig. 3. Typical deposition pattern of radiolabeled, jet-nebulized albuterol administered via tight-fitting mask (left) versus via a prototype aerosol hood (right). Pulmonary deposition is similar but there is less face deposition with the hood. (From Reference 7, with permission.)

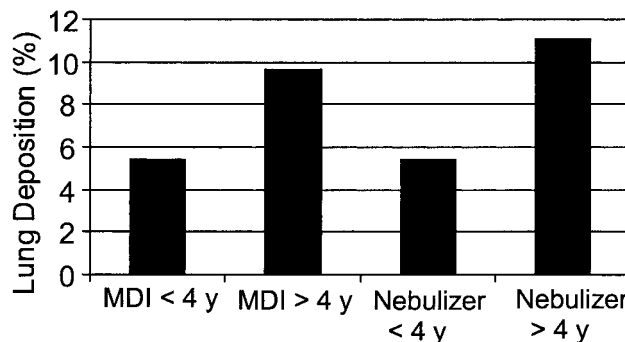


Fig. 4. Total lung deposition of radiolabeled albuterol administered via metered-dose inhaler (MDI, with holding chamber) or jet nebulizer to children (2–9 years old) with stable asthma. Mean lung deposition was 5.4% of the nebulized dose (108 μg) in children < 4 years old and 11.1% of the nebulized dose (222 μg) in children > 4 years old. (Adapted from data in Reference 9.)

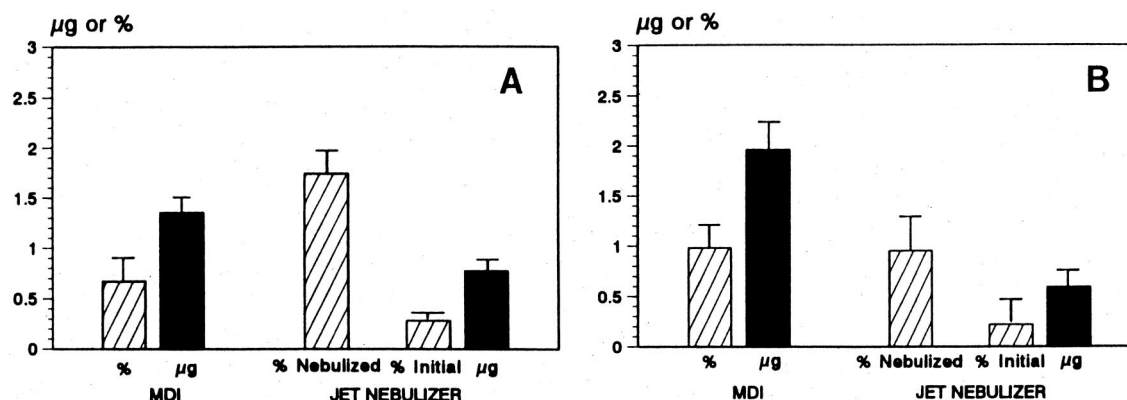


Fig. 5. Lung deposition in (A) nonventilated infants ($n = 13$) and (B) ventilated infants ($n = 10$). The values (which are mean \pm standard error of the mean) represent the percentage of the dose delivered and, for the nebulizers, also the percentage of initial nebulizer dose. The black bars indicate the amount of albuterol deposited in the lungs. (From Reference 10, with permission.)

In Vitro Models

In vitro models are the most common and convenient method for studying aerosol delivery during infant and pediatric mechanical ventilation. Similar to adult models in concept, infant models require different ventilation modes and parameters, and smaller-diameter circuits, ETTs, and test lungs. An intrinsic limitation of all available in vitro models is that they are unable to simulate exhalation of aerosol. Unlike human lungs and animal models, in which a portion of the inhaled aerosol is subsequently exhaled, in vitro models use an absolute filter or fluid barrier that collects all aerosol that passes the tip of the ETT. This results in a higher estimate of the inhaled respirable mass than in in vivo testing.¹¹

Cameron et al¹² ventilated an infant test lung model with pressure-limited ventilation, pressures of 20/2 cm H₂O, respiratory rate of 30 breaths/min, and I:E of 1:1. The gas flow was provided entirely through the nebulizer, with no humidification. Aerosol was collected on a filter distal to a 3.5-mm ETT. The nebulizer was placed 24 cm from the ETT. Deposition of aerosolized theophylline was greatest with the MAD2 nebulizer (Astra Medica) at 6 L/min (1.52%). With the Ultravent (Mallinckrodt) at 8 L/min deposition was 0.22%. With the Acorn (Medic Aid) at 8 L/min deposition was 0.88%. With the SPAG (Viratek) at 8 L/min deposition was 0.15%. With the Pulmosonic (Devilbiss) ultrasonic nebulizer with added gas flow of 8 L/min deposition was 0.8%. With a nebulized budesonide suspension deposition was greater with the MAD2 (2.72%) than with the Acorn (1.08%) or the Ultravent (0.06%). The nebulizer with the lowest gas flow through the ventilator consistently delivered the most aerosol to the filter.

Benson et al¹³ studied aerosol delivery from a MistyNeb (Airlife) jet nebulizer placed 60 cm from the ETT, with 3 ventilators: 1 volume-limited (Siemens Servo 900C) and 2

pressure-limited (Bourns BP 200, and Bear Cub BP 2001). They found no difference in delivery between the ETTs tested (2.5, 3.0, and 3.5 mm inner diameter) nor in peak inspiratory pressure (20–28 cm H₂O) or respiratory rate (40–80 breaths/min). Increasing the flow through the nebulizer (5, 7, and 10 L/min) increased the aerosol delivery (1.8, 2.2, and 2.7%, respectively). The volume-limited ventilator delivered more aerosol (2.47%) than the 2 pressure-limited ventilators (2.17 and 1.50%, respectively). The lung model used by Benson et al incorporated a 1,000-mL intravenous bag with 500 mL of NaCl 0.9% to collect drug. Presence of continuous flow with pressure-limited ventilation resulted in less deposition than the volume-limited ventilator, possibly because of the continuous flow through the circuit. Higher flow through the nebulizer may have generated smaller particles, resulting in greater deposition. Deposition was not affected by differences in ETT size, peak airway pressure, or respiratory rate.

Everard et al¹⁴ used a radiolabeled MDI aerosol of cromolyn sodium with a prototype 4×11 cm spacer and a Dräger Babylog 8000 pressure-limited ventilator, with standard settings (inspiratory flow 7.5 L/min, peak inspiratory pressure 30 cm H₂O, respiratory rate 30 breaths/min, I:E 1:1, V_T 11 mL, no mention of humidification) and a 3.0-mm ETT. More drug was deposited when the MDI was actuated before inspiration (1.54%) than after inspiration (0.83%). Changing I:E to 1:3 reduced deposition to 1.21 \pm 0.02% with actuation before inspiration and 0.24 \pm 0.03% after inspiration. Placing 10 cm of tubing between the spacer and ETT reduced filter deposition from 1.54% to 1.15% with smooth tubing and 0.89% with corrugated tubing. Deposition was higher with V_T of 16 mL (1.87%), and 22 mL (2.01%). The 2.5-mm ETT had higher deposition (1.80%) than the 3.0-mm ETT (1.54%). Actuating the MDI before inspiration is more efficient than actuation after inspiration. The highest deposition was achieved by

placing the MDI closer to the ETT and using a larger V_T and larger I:E (1:1).

In 1992 Arnon et al¹⁵ used a Sechrist ventilator with continuous flow of 8 L/min, pressures of 20/2 cm H₂O, respiratory rate of 30 breaths/min, V_T of 15 mL, and a nonhumidified circuit to ventilate a test lung through a 3.5-mm ETT. Two jet nebulizers (Ultravent, the aerosol particles from which have a mass median diameter of 1.2 μ m, and the MAD2, the aerosol particles from which have a mass median diameter of 1.9 μ m) were placed in the inspiratory limb, 10 cm from the Y-piece; 2 mg of budesonide in 4 mL of saline were nebulized for 5 min. Deposition was 0.02% with the Ultravent and 0.68% with the MAD2. In addition, 10 MDI puffs were actuated into a dry ventilator circuit at end-expiration via an Aerovent chamber and an Aerochamber MV15 chamber placed between the Y-piece and the ETT. With the Aerovent deposition was 3.6%. With the Aerochamber deposition was 14.2%.

Grigg et al¹⁶ used a Sechrist pressure-limited ventilator with peak inspiratory pressure of 20 cm H₂O and V_T of 15 mL. An ultrasonic nebulizer (Pentasonic) was placed in the inspiratory limb 10 cm from the ETT, and cromolyn was nebulized. Deposition was 1.3% of the dose, which is similar to deposition from an MDI actuated into an Aerochamber (1.7%) placed at the ETT. The authors correlated their *in vitro* model to *in vivo* administration, after establishing excretion rates of cromolyn in urine after direct instillation to the lung via bronchoscope.

Coleman et al¹⁷ used a Servo 900B ventilator to model a 4-kg infant, and delivered pressures of 60/5 cm H₂O, V_T of 55 mL, respiratory rate of 20 breaths/min, and duty cycle of 1:2 in a nonheated, corrugated circuit. Deposition from a MistyNeb jet nebulizer operated at 6.5 L/min and placed at the manifold position in the inspiratory limb was greater with continuous operation (targeting albuterol delivery of 10 mg/h over 3 h with an intravenous feed) (4.8%) than with intermittent therapy of 6 treatments representing a cumulative dose of 30 mg of albuterol (3.8%). Deposition decreased as flow through the nebulizer increased from 5 L/min (4.6%) to 6.5 L/min (3.7%) and 8 L/min (2.7%, $p < 0.03$). Deposition trended upward when I:E was increased from 1:2 (4.6%) to 1:1 (5.6%). Placing the nebulizer in the inspiratory limb 15 cm from the ETT yielded better deposition (5.1%) than placing it in the manifold position (4.0%). In a separate experiment 4 MDI puffs (360 μ g) of albuterol were administered through 4 actuator devices placed 15 cm from the ETT. Deposition was significantly greater with the ACE (14.5%) and Aerochamber MV15 (11.9%) than with the Aerovent (6.4%) and an inline MDI adapter (6.4%). In that study continuous nebulization delivered more drug than intermittent nebulization. Lower nebulizer flow gave greater deposition. Both MDI and nebulizer can deliver clinically important amounts of albuterol in these settings.

Garner et al¹⁸ used a Veolar (Hamilton) volume-limited ventilator with a pediatric breathing circuit to simulate a larger child, with a respiratory rate of 25 breaths/min, V_T of 250 mL, I:E of 1:3, dry and humidified circuits, and a 4.0-mm inner-diameter ETT. An albuterol MDI was actuated into an Airlife adapter and an Aerovent adapter. Deposition was greater with the Aerovent than the Airlife in both humidified (2.3 vs 1.3%, respectively) and dry circuits (15.5% vs 7.5%, respectively). There was no significant difference with change in ETT inner diameter (4.0 vs 6.0 mm) or length (19–25 cm). Use of a spacer and elimination of humidity improved deposition with pediatric settings.

Lugo et al¹⁹ used a VIP Bird ventilator to evaluate an expiratory-phase aerosol controller and determine the differences in aerosol delivery between continuous nebulization and on expiration-only nebulization in pediatric and neonatal ventilator circuits. Mean \pm SD aerosol delivery at the patient connection of the pediatric circuit was similar with the expiratory-phase aerosol controller ($1.5 \pm 0.002\%$) and continuous nebulization ($1.7 \pm 0.003\%$). Likewise, with the neonatal circuit deposition was similar with the expiratory-phase aerosol controller ($1.6 \pm 0.002\%$) and continuous nebulization ($1.5 \pm 0.002\%$). Unlike continuous nebulization, the expiratory-phase aerosol controller did not alter ventilation parameters during operation.

Pelkonen et al²⁰ used a Baby Bird pressure-limited ventilator and continuous gas flow of 12 L/min, pressures of 18/2 cm H₂O, respiratory rate of 40 breaths/min, V_T of 15 mL, I:E of 1:3, and a 3.0-mm inner-diameter ETT. A SideStream nebulizer was used to nebulize 1 mg of budesonide in a 2-mL volume and operated (1) continuously at 4.5 L/min in the inspiratory limb 8 cm from the ETT, (2) continuously between the circuit and the ETT, and (3) intermittently at the ETT. Drug was collected on a filter distal to the ETT and in the expiratory limb. Deposition was greater on the inspiratory filter with intermittent nebulization at the ETT (1.1%) than with continuous nebulization at the ETT (0.7%) or continuous nebulization 8 cm from the ETT (0.3%). Nebulization time was approximately 7 min with continuous nebulization and approximately 38 min with intermittent nebulization. Deposition on the expiratory filter (Fig. 6) was similar for both continuous-nebulization positions (15.6% in the inspiratory limb and 16.4% at the ETT) but markedly less with intermittent nebulization at the ETT (11.4%). Intermittent nebulization improved deposition and decreased the exhaled volume, but at the cost of a 5-fold increase in administration time.

Wildhaber et al²¹ used a Siemens Servo ventilator to simulate ventilation of 4-kg, 15-kg, 50-kg and 70-kg patients. In all cases albuterol was administered from a hydrofluoroalkane-propellant MDI actuated into either an inline nonchamber adapter (Baxter), a small chamber (Aerochamber MV), or a large chamber (Nebuhaler). All

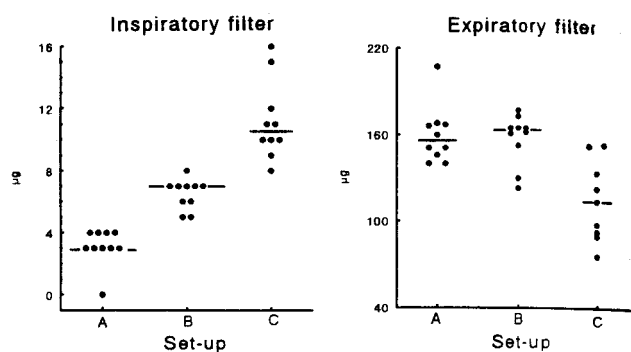


Fig. 6. Mass of budesonide deposited in inspiratory and expiratory filters. A: 1 mg of budesonide nebulized continuously and delivered into the inspiratory limb. B: 1 mg of budesonide nebulized continuously and delivered between the Y-piece and the endotracheal tube. C: Nebulized intermittently and delivered between the Y-piece and the endotracheal tube. The horizontal lines represent the medians. (From Reference 20, with permission.)

devices were soaked in deionizing detergent to reduce electrostatic charge and were operated between the Y-piece and the ETT. The parameters for the 4-kg model were V_T of 40 mL, pressures of 20/4 cm H_2O , respiratory rate of 30 breaths/min, no humidification, and a 4.0-mm ETT. Deposition was greater with the Aerochamber MV (14.3%) than with the larger Nebuhaler (7.2%), and performance with either spacer was more efficient than with the non-chamber adapter (1.9%). The smaller chamber was more efficient than the larger chamber or inline adapter. Relatively high deposition ($> 14\%$) is possible in an infant model of mechanical ventilation.

Avent et al²² used a Servo 900C ventilator with a 120-cm humidified, heated-wire circuit to simulate infant ventilation, with pressures of 30/4 cm H_2O , respiratory rate of 40 breaths/min, inspiratory time 0.4 s, and a 3.5-mm ETT. A Whisper Jet nebulizer was placed in the inspiratory limb 60 cm from the ETT and operated for 15 min at 5 L/min. An Aerochamber was placed between the Y-piece and the ETT. Total delivered dose was greater with the nebulizer, but deposition was greater with the albuterol MDI (1.96%) than with the nebulizer (1.26%). However, deposition with a beclomethasone MDI was less (0.51%).

In another study Avent et al²³ used a similar model with a Bear Cub ventilator, a humidified, heated-wire circuit, pressures of 20/2 cm H_2O , respiratory rate of 40 breaths/min, and inspiratory time of 0.5 s. They compared albuterol delivery with an MDI using an Aerochamber and an inline adapter placed at the ETT. The Aerochamber provided 18-fold greater delivery than the inline adapter (2.17% vs 0.12%, $p = 0.001$).

Lugo et al¹⁹ used a Bird VIP ventilator, a humidified, heated-wire circuit, pressures of 25/4 cm H_2O , respiratory rate of 30 breaths/min, I:E of 1:2, a flow 9 L/min, a V_T of 7 mL, and a 3.0-mm ETT. A MistyNeb nebulizer was

operated at 6 L/min to nebulize 3 mL of 0.5% albuterol, with the humidifier on standby during administration. The nebulizer was placed in the inspiratory limb 125 cm from the Y-piece (ie, at the ventilator) and then tested at 30 cm from the Y-piece. Two MDI albuterol formulations (chlorofluorocarbon propellant and hydrofluoroalkane propellant) were administered via ACE spacer placed between the Y-piece and the ETT. The MDI/spacer arrangement was also administered with a manual resuscitation bag with similar pressure and respiratory rate. With the nebulizer placed at the ventilator, the deposition was 0.15%. With the nebulizer placed 30 cm from the Y-piece, the deposition was 0.16%. With the MDI/spacer the deposition was 3.82–5.66%. With the chlorofluorocarbon MDI deposition was greater with the ventilator (4.79%) than with the manual resuscitation bag (3.82%). The hydrofluoroalkane-propellant MDI had marginally greater deposition than the chlorofluorocarbon formulation, and the deposition was similar with the ventilator (5.66%) and the manual resuscitation bag (5.45%).

Garner et al²⁴ used a VIP Bird ventilator to compare albuterol delivery during conventional intermittent mandatory ventilation, assist-control ventilation, and assist-control with flow synchronization. The model simulated an intubated neonate with a spontaneous respiratory rate of 40, 60, or 80 breaths/min and compliance and resistance values of bronchopulmonary dysplasia. Albuterol (2.5 mg) was administered with a T Up-Draft II Neb-U-Mist nebulizer attached to a 12.75-cm (10-mL) reservoir of circuit tubing. There were no significant differences in percentage of albuterol delivered among the 3 modes or the 3 spontaneous respiratory rates. The mean \pm SD deposition values were: intermittent mandatory ventilation $0.11 \pm 0.04\%$; assist-control $0.12 \pm 0.03\%$; assist-control with flow synchronization $0.10 \pm 0.04\%$; 40 breaths/min $0.11 \pm 0.03\%$; 60 breaths/min $0.11 \pm 0.04\%$; 80 breaths/min $0.11 \pm 0.05\%$ ($p > 0.05$).

Habib et al²⁵ modeled a 15-kg child, using a volume-cycled VIP Bird ventilator, nonhumidified circuit, V_T of 250 mL, respiratory rate of 25 breaths/min, positive end-expiratory pressure of 3 cm H_2O , I:E of 1:2.5, flow of 25 L/min, and a 4.0-mm ETT to test the difference between delivering albuterol via helium-oxygen mixture (70% helium) and nitrogen-oxygen mixture (70% nitrogen). Albuterol administered via MDI and Aerochamber placed between the Y-piece and ETT delivered 12% with the nitrogen mixture and 20% with the helium mixture.

Garner et al²⁶ simulated a 3-year-old child, using a SensorMedics 3100A high-frequency-oscillation ventilator, a humidified circuit, a 4.5-mm ETT, mean airway pressure of 28 cm H_2O , operating frequency of 10 Hz, pressure amplitude of 55 cm H_2O , and an inspiratory time of 30%. Delivery of albuterol via MDI/Aerochamber was 0.55% and via inline adapter it was 0.67%. Deposition with the

Table 3. Aerosol Deposition Efficiency in Animal Models

Year	Researchers	Animal	Aerosol Device	Lung Deposition (%)
1986	Flavin et al ³²	Rabbit	Nebulizer	0.19–1.96
1991	Cameron et al ¹²	Rabbit	Nebulizer	0.05–0.11
1992	Everard et al ¹⁴	Rabbit	MDI	1.5–2.0
1992	O'Callaghan et al ²⁹	Rabbit	MDI	1.2–1.9
1997	Fok et al ³³	Rabbit	MDI	0.23–0.5
1997	Fok et al ³⁰	Rabbit	MDI, Nebulizer	0.22–3.05
2002	Dubus et al ³⁵	Monkey	Nebulizer	0.5–13.9

MDI = metered-dose inhaler.

inline adapter was lower at a respiratory frequency of 5 Hz (0.28%) than 15 Hz (0.36%). Deposition was also lower with inspiratory times of 40% (0.26%) and 50% (0.26%).

Fink et al²⁷ used a SensorMedics 3100A high-frequency-oscillation ventilator, a humidified circuit, a 5-mm ETT, respiratory frequency of 8.0 Hz, inspiratory time of 33%, amplitude of 25 cm H₂O, and mean airway pressure of 20 cm H₂O. Two pneumatic nebulizers, the MistyNeb and VixOne, were operated at 6 L/min of oxygen. Also tested was an electronic micro-pump nebulizer, the Aeroneb Pro, which requires no gas flow. All were operated in the inspiratory limb 10 cm from the ETT. The Aeroneb Pro delivered more albuterol (23.2%) to the end of the ETT than the MistyNeb (8.4%) or the VixOne (7.8%, $p < 0.02$). Both of the pneumatic nebulizers altered mean airway pressure during operation.

Kelly et al²⁸ used a Servo 900B volume-limited ventilator, a dry circuit, pressures of 60/5 cm H₂O, respiratory rate of 20 breaths/min, V_T of 55 mL, I:E of 1:2, and a 3.5-mm ETT, and tested a small-volume MistyNeb nebulizer with infusion pump versus a large-volume Heart nebulizer. The nebulizers were placed at the ventilator manifold in the inspiratory limb and set to deliver 10 mg/h of albuterol continuously over 8 hours on 6 consecutive days. The small-volume nebulizer delivered 5.75% and the large-volume nebulizer delivered 4.12% ($p < 0.025$). The small-volume nebulizer had greater day-to-day variability, whereas output from the large-volume nebulizer dropped off dramatically near the end of 8 hours.

In Vivo Animal Studies

Because of the difficulties of performing deposition studies in infants, small mammals have been used as models. However, the relevance of these models is limited because, though the airways of a 2-kg animal are of similar diameter to a newborn infant, the airway anatomy is substantially different and the animals do not have underlying

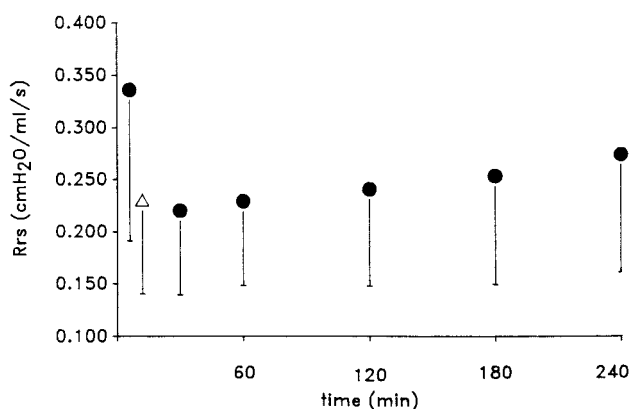


Fig. 7. Duration of effect of 200 µg albuterol on total resistance of the respiratory system (R_{rs}). Values are mean \pm SD. The open triangle represents data obtained on the preceding day, 10 min after 200 µg albuterol. (From Reference 37, with permission.)

disease. Lung deposition has been consistently low in the animal-model studies.^{12,29–34} With anesthetized rabbits intubated with a 3.0-mm ETT, deposition of an aerosol administered via spacer in the inspiratory limb or directly into the ETT was 0.2–0.4% of the emitted dose.^{29,30} In conditions of uncontrolled ventilation in nonparalyzed rabbits the maximum deposition was 5% of the emitted dose.³¹ With a 3.5-mm ETT and jet nebulization lung deposition was $< 1\%$.^{12,32,33} Lung deposition was slightly improved by using a small cup of 10 mL with an ultrasonic nebulizer³³ and by inspiration-synchronized nebulization rather than continuous nebulization.¹⁰

Table 3 summarizes the animal model studies of aerosol deposition.

Flavin et al³² used a Bourne LS104 volume-limited ventilator to deliver aerosol of ^{99m}Tc-labeled sulfur colloid to tracheotomized rabbits. Deposition with a standard jet nebulizer ($0.19 \pm 0.10\%$) was significantly less than with a submicronic nebulizer ($1.96 \pm 1.19\%$, $p < 0.0001$).

Cameron et al¹² quantified the effect of changing ventilator variables. Twenty-three freshly sacrificed rabbits

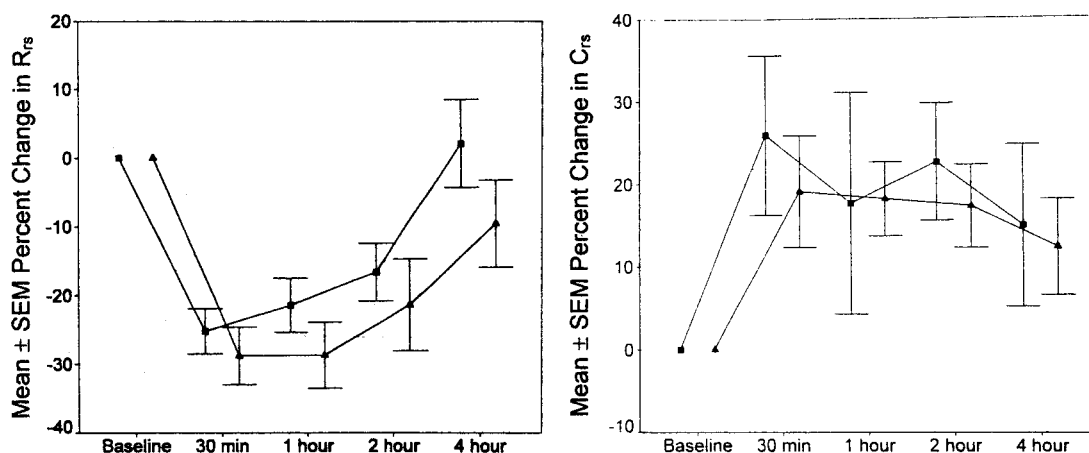


Fig. 8. Mean percent change in total resistance (R_{rs}) and total compliance (C_{rs}) of the respiratory system following administration of albuterol via metered-dose inhaler and via nebulizer in 11 ventilated infants. (From Reference 39, with permission.)

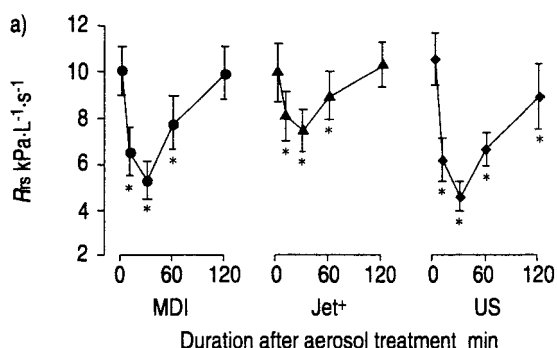


Fig. 9. Total resistance of the respiratory system (R_{rs}) before and at 15, 30, 60, and 120 min after albuterol via metered-dose inhaler (MDI), jet nebulizer (Jet), and ultrasonic nebulizer (US). * Post-treatment R_{rs} was significantly lower than pre-treatment R_{rs} ($p < 0,0001$). (From Reference 40, with permission.)

(1.15–1.9 kg) were ventilated via tracheostomy with a Neovent pressure-limited, time-cycled ventilator. An aerosol of ^{99m}Tc -labeled pertechnetate from an Ultravent nebulizer was fed into the proximal ventilator tubing. Two 3-min nebulizations at “standard settings” were followed by 2 nebulizations at different pressure, respiratory frequency, gas flow, I:E, or position of the nebulizer in the circuit. Each nebulization was followed by a 3-min gamma-camera image, and total deposited radioactivity was measured in excised lungs and trachea. The images indicated good peripheral aerosol deposition. At the standard settings lung deposition averaged 2.8%. This was decreased markedly by reducing V_T (ventilator pressure) and the residence time of the aerosol (I:E). Reducing the gas flow decreased deposition slightly, presumably because of increased particle size and marginally reduced V_T .

Fok et al³⁰ delivered 5 puffs of radiolabeled albuterol from an MDI via an MV15 Aerochamber to intubated and ventilated rabbits that were either paralyzed with intrave-

nous pancuronium and ventilated at a rate of 30 breaths/min or under light anesthesia (without paralysis) at a rate of 10 breaths/min. The spontaneously breathing rabbits had significantly greater lung deposition than the paralyzed rabbits (0.510 ± 0.076 vs $0.226 \pm 0.054\%$, $p = 0.0094$). Deposition in the airway, ETT, and ventilator circuit did not differ significantly.

Fok et al³³ used a Siemens 300 ventilator and a Bourne BP200 ventilator, a heated, humidified infant circuit, pressures of 12/2 cm H_2O , respiratory rate of 30 breaths/min, inspiratory time of 0.5 s, V_T of 7–10 mL/kg, and a 3.5-mm ETT to deliver radiolabeled aerosol to 31 rabbits (average weight 3 kg). The MDI/Aerochamber was placed between the Y-piece and ETT. The jet nebulizer and the ultrasonic nebulizer were filled with either 10 mL or 20 mL of medication. Both nebulizers were placed in the inspiratory limb. Mean \pm SEM pulmonary deposition (as a percentage of the dose) was: MDI/Aerochamber $0.22 \pm 0.05\%$; jet nebulizer $0.48 \pm 0.05\%$; ultrasonic nebulizer with 10 mL $3.05 \pm 0.49\%$; ultrasonic nebulizer with 20 mL $0.90 \pm 0.13\%$. Deposition with the ultrasonic nebulizer with 10 mL was significantly higher than the other systems ($p < 0.05$). Dynamic scintigraphy showed that, among the nebulizers, ultrasonic nebulizer with 10 mL continued to deliver medication for longer than either the jet nebulizer or the ultrasonic nebulizer with 20 mL.

Dubus et al³⁵ created a model of infant ventilation with 4 intubated macaques (2.6 kg), a Dräger Babylog ventilator, a 3.0-mm ETT, respiratory rate of 40 breaths/min, pressures of 20/2 cm H_2O , I:E of 1:2, and 0.30% oxygen. They nebulized 3 mL containing 30 millicuries of ^{99m}Tc -DTPA, using a MistyNeb jet nebulizer placed in the inspiratory limb of a dry neonatal circuit, 10 cm from the Y-piece. Deposition was 0.5% (range 0.4–1.3%). With a 0.5-mL volume nebulized with an Aeronex Pro, deposition was 12.6% (range 9.6–20.6%) ($p = 0.006$). Duration of

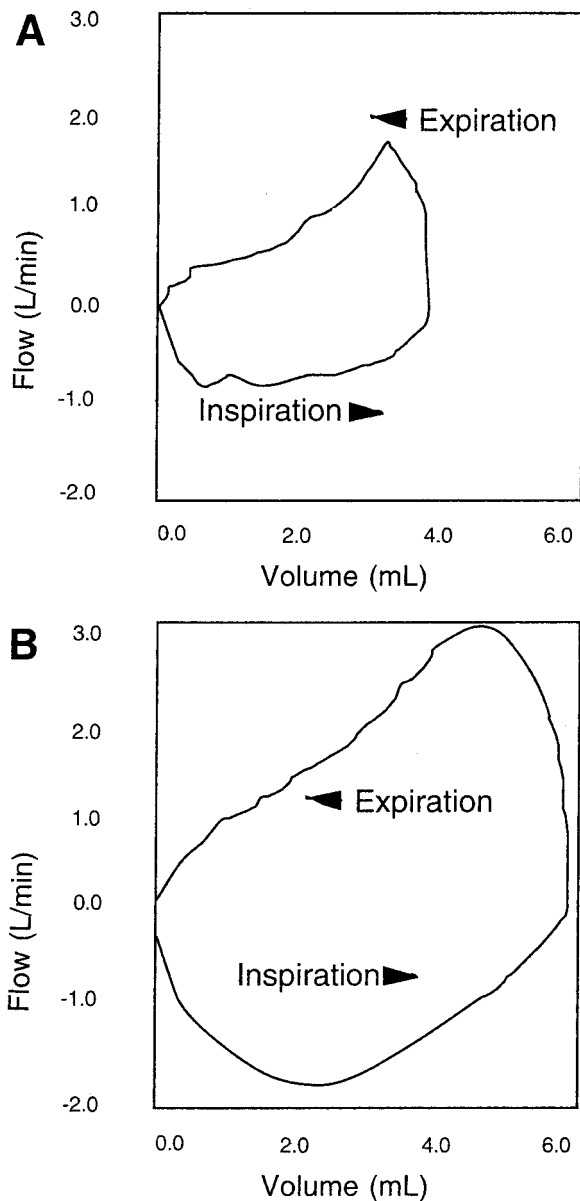


Fig. 10. Tidal flow-volume loops based on mechanical breaths in an infant with a positive response to inhaled bronchodilators (A) before (ie, at baseline) and (B) 20 min after administration. (From Reference 42, with permission.)

delivery was shorter with the Aereoneb Pro (2 min) than with the Mistyneb (10 min) ($p < 0.001$). The efficiency of the jet nebulizer was consistent with other animal models and in vivo infant studies, but deposition with the Aereoneb Pro was greater than previously reported from a nebulizer in infant ventilation.

Outcome Studies in Ventilated Infants

The relatively low efficiency of aerosol deposition during infant ventilation may be misleading, in that a small

absolute lung dose provides a larger dose/kg of body weight than in adults. It is more clinically relevant to evaluate the physiological effect of a pharmacologic aerosol than to dwell on scant deposition data.

Bronchodilators

Rotschild et al³⁶ studied 20 ventilator-dependent infants (weighing $< 1,500$ g) and found that 2.5 mg of aerosolized albuterol improved static compliance significantly more than placebo and decreased P_{CO_2} .

Denjean et al³⁷ reported a dose-response study in which they administered 1 or 2 MDI puffs of albuterol via manual ventilation over 30 seconds and found that 30 min after treatment the total compliance of the respiratory system had increased 67% and the total resistance of the respiratory system had decreased 33% (Fig. 7).

With 8 ventilated infants Pfenninger and Aebi³⁸ found no difference in patient response between 10 $\mu\text{g}/\text{kg}$ of intravenous albuterol and 200 μg albuterol via MDI/spacer adapter.

With 11 ventilated infants Torres et al³⁹ compared delivery of albuterol via hand ventilation with nebulizer (1.5 mg in 3 mL saline) and via MDI/chamber (360 μg). Change in total resistance and total compliance of the respiratory system persisted for 2 hours after administration, but not at 4 hours, and there was no difference between the methods (Fig. 8).

Fok et al⁴⁰ compared administration of 200 μg of albuterol from an MDI/Aerochamber (with valve removed), a Siemens ultrasonic nebulizer, and 2 jet nebulizers (Side-Stream and Hudson) operated at 6 L/min. The MDI and ultrasonic nebulizer provided greater reductions in total resistance of the respiratory system than did either jet nebulizer. The ultrasonic nebulizer trended toward a greater bronchodilator effect than the MDI (Fig. 9).

Sivakumar et al⁴¹ obtained similar results in premature infants who required ventilation after 7 days of age. Albuterol via MDI/spacer increased passive respiratory system compliance more than did albuterol via low-flow nebulizer (34% vs 11%, $p < 0.02$).

Holt et al⁴² demonstrated the use of flow-volume loops and lung function testing to differentiate infants' response to bronchodilators during mechanical ventilation (Fig. 10).

Inhaled Steroids

Arnon et al⁴³ evaluated the effects of 600 μg of inhaled budesonide via nebulizer (twice a day) in ventilator-dependent preterm infants at 14 days of age. The steroid-treated infants required lower airway pressures and lower inspired oxygen concentration than did the control infants after 4 days of therapy (Fig. 11). However, there was no

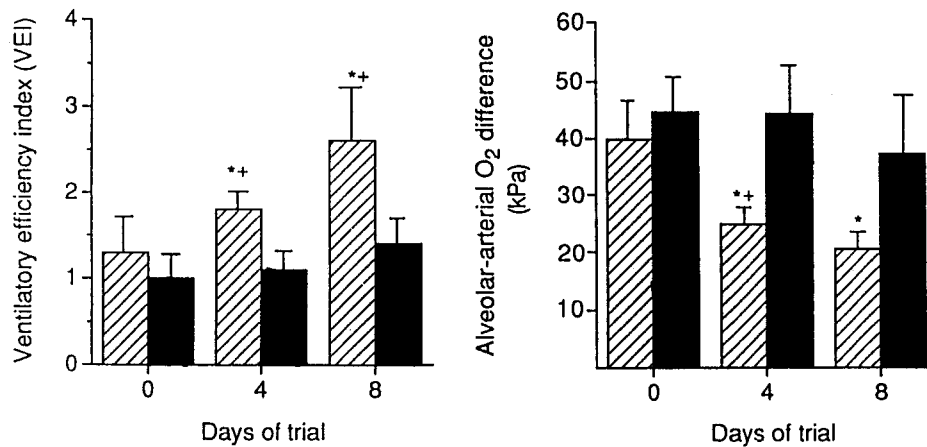


Fig. 11. Ventilatory efficiency index and alveolar-arterial oxygen difference before, during, and at end of a trial with budesonide (hatched bars) and placebo (black bars). Values are mean \pm standard error of the mean. * Significantly different ($p < 0.05$) from pretreatment values. + Significantly different ($p < 0.017$) from placebo group. (From Reference 43, with permission.)

difference in the extubation rate during the 7 days of treatment.

Giep et al⁴⁴ studied the effects of 350 μg of inhaled beclomethasone via MDI in 19 ventilator-dependent infants greater than 2 weeks of age and had a placebo group. Six of the 10 infants treated with beclomethasone were extubated during the study period, whereas only 1 of the 9 control subjects was extubated.

Zimmerman et al⁴⁵ conducted a placebo-controlled trial to evaluate the efficacy of 350 μg MDI beclomethasone on pulmonary function in 39 ventilated infants at risk of bronchopulmonary dysplasia, starting on day 1 of life and tapering the dose over 12 days. The treatment group had fewer mechanical ventilation days (20 ± 16 vs 37 ± 19 d) ($p = 0.004$) and needed less supplemental oxygen at 30 days of age (65% vs 100%, $p = 0.005$).

Cole et al⁴⁶ reported a randomized, double-blind, placebo-controlled trial of the efficacy of inhaled beclomethasone in 253 premature, mechanically ventilated infants at high risk of bronchopulmonary dysplasia. The initial dose was calculated to deliver 40 $\mu\text{g}/\text{kg}/\text{d}$ for the first week, 30 $\mu\text{g}/\text{kg}/\text{d}$ for the second week, 15 $\mu\text{g}/\text{kg}/\text{d}$ for the third week, and then 10 and 5 $\mu\text{g}/\text{kg}/\text{d}$ during the fourth week. Inhaled beclomethasone therapy was associated with less use of systemic glucocorticoids and less mechanical ventilation at 28 days of age. However, the frequency of bronchopulmonary dysplasia (as measured by oxygen dependence at 28 days of age or 36 weeks corrected gestational age) did not differ between the 2 groups.

Fok et al⁴⁷ studied 53 ventilated preterm infants born at < 32 weeks gestational age (birth weight < 1.5 kg) with respiratory distress syndrome after treatment with surfactant. They administered inhaled fluticasone propionate, starting on day 1 of life, with a dose of 1 mg/d, in 2 divided doses, for 14 days. The treatment group had sig-

nificantly more early extubations (63% vs 31%) and better improvement in respiratory compliance during the first 14 days of life than did the placebo group.

Jonsson et al⁴⁸ studied 27 very-low-birthweight infants (gestational age 26 weeks, birth weight 805 g) who required mechanical ventilation on day 6 of life or continuous positive airway pressure and $\geq 30\%$ inspired oxygen. They delivered 500 μg budesonide twice a day or placebo with a dosimetric jet nebulizer and found that infants who received budesonide were more often extubated during the 15-day study period and had a greater oxygenation-index improvement above baseline.

A recent meta-analysis⁴⁹ concluded that inhaled steroids have only very small effects on the occurrence of chronic lung disease in ventilator-dependent infants, probably because of inappropriate aerosol delivery methods. Indeed, the use of an MDI with spacer may be more efficient than a conventional jet nebulizer for delivering albuterol or budesonide to neonates.¹⁹

New Directions and Devices

As we have come to understand the limitations and potential of existing and developing technology, it is clear that we can substantially improve the efficiency of aerosol deposition in ventilated infants. For example, nebulizers with residual volumes of microliters instead of milliliters reduce the gap between the initial nebulizer dose and the dose nebulized. The ability to control particle size, placement, and precise patterns of aerosol generation is the key to improving efficiency. As we learn to consistently exceed single-digit deposition in neonates, there is the opportunity to develop a broad variety of drugs to treat that patient population (Table 4).

Table 4. Drug Candidates for Aerosol Delivery to Ventilating Infants

<i>Local effect</i>
Steroids
Antibiotics
Antivirals
Surfactants
Diuretics
Prostacyclin
<i>Systemic effect</i>
Prostaglandins
Sedatives
Vasoactive medications

Summary

Though delivering aerosol to infants poses substantial challenges, it is clear that existing systems can provide effective inhalable therapy, including bronchodilators to anti-inflammatories, and anti-infectives such as ribavirin. To overcome the problem of low aerosol deposition and large interpatient and inpatient variability of deposition we must understand and be aware of the variables that affect deposition. Only when we can consistently administer aerosolized medications to ventilated infants will there be active development of inhalable medications for infants.

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