

## Clinician's Dilemma: Aerosol Delivery to Neonates

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### Introduction

Aerosol delivery to the neonate has long been an area of controversy, with strong division in clinician opinions based on a sparseness of evidence. The practice of aerosol administration to neonates and small infants largely evolved based on anecdotal evidence and attempts to achieve observed therapeutic or adverse effect. The delivery efficiency of aerosol from pMDIs and jet nebulizers has been demonstrated to be so small, and the inconvenience of integrating these devices into the ventilator circuit so great, that many clinicians avoid delivering aerosols to neonates requiring mechanical ventilatory support.<sup>1</sup>

Because of the difficulties of using radiation with small infants, only one study has quantified aerosol delivery in infants less than 4 kg, on and off the ventilator. As this study had similar results as animal models under similar conditions, we have been left to rely on in vitro models and animal studies to quantify the impact of variable upon aerosol delivery during infant ventilation. These studies suggest that selection of appropriate technology may improve efficiency and consistency of aerosol drug delivery to neonates. This promise of improved efficiency with newer technology must be tempered by the clinician's responsibility to carefully titrate doses to desired effect, with close monitoring to avoid administration of potentially toxic local and systemic levels of drugs. In addition, attention to a few key issues can substantially reduce the risk of aerosol delivery to the neonate.

### Why is the Neonate Different

The neonate typically has a fully defined conducting airway at birth; however, the size of those airways and the number of alveoli increase dramatically in the first year of life. The low tidal volume, vital capacity, functional residual capacity, and short respiratory cycles of neonates result in limited amounts of

aerosol inhaled with low residence time for small particles in the lung, resulting in a further decrease in pulmonary deposition. Resting respiratory rate decreases with age as tidal volume and minute ventilation increase, resulting in a 5-10-fold increase in aerosol deposition by age 6 years.<sup>2-4</sup>

Many variables have been shown to impact aerosol delivery to the neonate (Table 1).<sup>5</sup> Because of the small tidal volumes and high respiratory rates required, ventilators designed to support the neonate are often time or pressure cycled, with a continuous flow of gas circulating through the ventilator circuit. This flow tends to dilute aerosols and sweep them past the patient and into the expiratory limb of the ventilator circuit.

Data regarding inhaled particle mass, lung deposition, and regional distribution of aerosols in neonates is limited. Pulmonary deposition of medical aerosol from either a jet nebulizer or pMDIs to neonates may be 0.5 - 1% of the nominal dose,<sup>3</sup> compared to 8-22% in older children and adults.<sup>4,5</sup> With the absence of data in infants, we have had to rely on in vitro and animal models to assess the impact of various technologies and delivery variables for aerosol delivery efficiency (Table 2). These studies show that while pMDI and jet nebulizers deliver less than 1% of dose to the lung of a neonate size animal, that ultrasonic nebulizers may deliver up to 3%,<sup>10</sup> and vibrating mesh nebulizers can deliver up to 12.9%.<sup>12</sup> While increased efficiency of aerosol delivery to the neonate may offer new opportunities, the use of such technologies must be tempered with caution by the clinician to assure the patient's safety.

### Should dosing be reduced for neonates?

I recall that in the first Neonatal Pediatric Specialty (NPS) exam offered by the National Board of Respiratory Care (NBRC), no less than four questions concerned how to reduce the dose of terbutaline for administration to infants based on body weight. The assumption that smaller patients need smaller doses of aerosol may be intuitive, but is not supported by any firm evidence.

In the case of the neonate receiving a standard unit dose of

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albuterol sulfate (2500 µg) with a deposition efficiency of 0.5%, the lung dose of 12.5 µg in a 4 kg infant would be 3.1 µg/kg. In contrast, typical 10% deposition (250 µg) in a 70 kg adult would provide a similar 3.6 µg/kg.<sup>7</sup> It appears that the low efficiency of deposition in neonates may effectively produce a similar dose per kg. Consequently, reduction of the dose based on some arbitrary basis may have substantially reduced delivery below a therapeutic threshold.

Anecdotally, this low deposition in neonates appears to provide a comparable safety and efficacy profile similar to that in adults. Consequently, rationales to reduce doses for infants and small children with beta-adrenergic bronchodilators that have not been well substantiated in the literature should not form the basis of institutional practice.

That said, in the absence of empirically based dosing guidelines for neonates, the AARC clinical practice guidelines recommended that any bronchodilator administered by aerosol to a neonate be titrated to effect, with close monitoring.<sup>13</sup> This is especially relevant when adopting aerosol technology with potentially greater efficiency than the commonly used standard jet nebulizer or pMDI.

### Nebulizer placement

Standard jet nebulizers, ultrasonic nebulizers and pMDI spacers may have internal volumes ranging from 15-130 mL. Due to the low volumes being administered to neonates (5-15 mL), placement of these devices at the airway would result in the infant rebreathing through greatly increased mechanical deadspace and being at high risk of becoming hypercarbic. Consequently, nebulizers are typically placed in the inspiratory limb of the ventilator circuit. Due to the size and weight of the nebulizers, they are placed at least 10 cm away from the patient



Figure 1: The Aeroneb Solo (Aerogen) is a vibrating mesh nebulizer designed for use with intermittent (up to 30 minutes treatments) and continuous nebulization.

wye, and on some occasions back near the ventilator. While there is some evidence in adult ventilator circuits that placement of jet nebulizers near the ventilator may improve delivery,<sup>14</sup> there is little rationale or evidence to suggest similar placement may increase delivery to the neonate. In adult ventilator circuits, with an internal volume of 500-600 mL, a jet nebulizer can charge the inspiratory limb so that a bolus, rich in aerosol, can be inhaled with a typical 500 mL breath. Even though an infant ventilator circuit has a smaller internal volume (< 200mL), tidal breaths are less than 10% of that internal volume. Consequently, placement of the nebulizer at around 10-20 cm from the wye may offer a more appropriate volume for supplying an aerosol rich bolus with each breath.

**Table 1: Factors that Alter Aerosol Delivery in the Ventilated Neonate**

Ventilator type	Pressure vs Volume Limited
	Continuous flow of gas through circuit
	Respiratory rate
	Tidal volume
	Inspiratory flow rate
	I:E ratio
Circuit type	Diameter
	Length
	Adapters
Airway	Size
	Type
Nebulizer	Type
	Fill Volume
	Particle size
	Aerosol Output rate
	Gas flow rate
	Position in the ventilator circuit
pMDI	Adapter/spacer used
	Timing of actuation
	Position in the ventilator circuit

### Continuous nebulization

One method to compensate for low aerosol delivery efficiency has been to use a continuous feed through an infusion set into a nebulizer. This method can allow dosing of aerosol at different rates, by adjusting the flow of drug/unit of time into the nebulizer. Researchers have reported using continuous nebulization to deliver drugs ranging from bronchodilators to prostacyclins.

Continuous nebulization options have long been available with jet and ultrasonic nebulizers. Recently, a vibrating mesh nebulizer (Figure 1) has been introduced with this capability.

Care must be taken to assure that the drug is not loaded into the nebulizer faster than it leaves the nebulizer as aerosol. Overflowing the nebulizer reservoir can reduce aerosol efficiency and increase the amount of unwanted fluid in the ventilator circuit.

### Potential for contamination during nebulization

Aerosol delivery has been associated with increased incidence of pulmonary infection in the adult ICU. Although no reports have established that relationship with neonates, the clinician should be aware of a few obvious but common practices that may place their patients at risk.

Evidence suggests that patients manage to contaminate their ventilator circuit within a matter of minutes or hours. Any

**Table 2: Deposition Efficiency of Animal Models**

1986	Flavin (6)	Rabbit	Nebulizer	0.19 – 1.96%
1991	Cameron (7)	Rabbit	Nebulizer	0.05 – 0.11%
1992	Everard (8)	Rabbit	pMDI	1.5 – 2.0%
1992	O'Callaghan (9)	Rabbit	pMDI	1.2 – 1.9%
1997	Fok (10)	Rabbit	pMDI	0.23 – 0.5%
1997	Fok (11)	Rabbit	pMDI, Nebulizer	0.22 – 3.05%
2002	Dubus (12)	Monkey	Nebulizer	0.5 – 13.9%

condensate that forms in the ventilator circuit can be contaminated. Even in well controlled heated wire circuits, the gas source used to drive a jet nebulizer is not heated, resulting in cooling of the gas mixing with aerosol in the ventilator circuit, which results in some level of condensate formation. Fluid in ventilator circuits tends to collect in the lowest point of the circuit. Unfortunately, the lowest point in the inspiratory limb of an infant vent circuit may be the medication reservoir of the nebulizer. Jet and ultrasonic nebulizers are placed below the lumen of the ventilator circuit. In addition to creating aerosol, these nebulizers may act as a gravity-dependent water trap, collecting contaminated condensate and even secretions that enter the inspiratory limb. Even with unit dose of medication, it is not uncommon for clinicians to come back to the bedside after 15-30 minutes of nebulization to find more fluid in the nebulizer than when they started. It is difficult to rationalize that this is a good thing for the patient. Aerosolizing potentially contaminated condensate during mechanical ventilation would appear to present a hazard to the mechanically ventilated neonate. This hazard can be avoided with the use of pMDIs or vibrating mesh nebulizers. In both cases, the medication reservoir is a superior position to the lumen of the ventilator circuit, and separated from ventilator circuit. Gravity is much less likely to bring condensate in contact with the aerosol generator. Even if it does, the medication is less likely to be contaminated with condensate or secretions prior to nebulization.

It is incumbent upon clinicians to base their practice on a combination of the best available science and good common sense. As technology improves the ability to deliver aerosols to patients, we must use our best judgment tempered with close monitoring to assure safe and effective respiratory care.

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