Challenges of aerosol therapy among mechanically ventilated infants

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Abstract
Aerosolized medications are routinely used in neonatal and pediatric intensive care units (NICUs and PICUs, respectively) in newborn infants and small children on and off ventilatory support. However, delivery of aerosolized medications using currently available technology for use in infants and small children is suboptimal in that the delivery devices employed have not been developed with rigorous evaluation of efficacy and safety in these populations and optimized for targeting their small airways. Significant physiological and physical challenges exist when delivering aerosolized medications to newborn infants and small children. These include high respiratory rate in these patients, smaller airway diameter, low tidal volume and functional residual capacity, and a shortened drug particle residence time. These variables, individually and collectively, can diminish delivery of inhaled aerosols to the lower airways in these populations. Moreover, the ability to adequately study pulmonary delivery, absorption, metabolism, and excretion of aerosolized medication in these populations is limited.

Keywords: aerosols, infant, mechanical ventilation

Introduction
Aerosols have proven to be an effective form of drug delivery. Nevertheless, the development of devices as well as medical agents for aerosolization to treat intubated and mechanically ventilated infants still presents a significant challenge [1]. Low tidal volumes and functional residual capacity, high respiratory rates, a shortened particle residence time and smaller airway diameters account for the diminished delivery of inhaled aerosols to the lower airways in these infants [2-4]. There are a limited number of clinical deposition studies in the neonatal population because of the inability to use radio labeled aerosols [5]. However, despite the paucity of clinical data, aerosols have been used to treat critically ill newborn infants without a clear understanding of the optimal aerosol delivery system, the drug deposition pattern in the lung and the dose/response relationship for aerosolized medications. As multicenter questionnaire based study showed aerosolized medications are administered to infants with ventilator support as part of routine therapy [6].

Aerosolized drugs used for ventilated infants
A wide variety of aerosolized medications have been studied in critically ill infants, demonstrating little to no benefit. Shah and co-workers published a review in the Cochrane Library on early administration of inhaled corticosteroids for preventing chronic lung disease (CLD) in ventilated very low birth weight infants. The meta-analysis of seven trials found no evidence that the early use of inhaled steroids prevents the development of CLD [7]. All of the studies included in this meta-analysis utilized metered dose inhalers (MDI) except one study by Jonsson et al., which used a dosimetric jet nebulizer for corticosteroid aerosol generation [8].

There have been several small clinical studies conducted focusing on the use of aerosolized diuretics for treatment of infants with developing or established CLD. A recently updated Cochrane Review concluded that in preterm infants older than 3 weeks of life with CLD, administration of a single dose of aerosolized furosemide improved pulmonary mechanics. However, in view of the lack of data from randomized trials concerning effects on important clinical outcomes, routine or sustained use of aerosolized loop diuretics in infants with (or developing) CLD was not recommended [9]. Of the 8 studies comprising this review only 4 indicated the type of aerosol generator used: jet and ultrasonic.

The Cochrane Library also reviewed the use of aerosolized bronchodilators for the prevention and treatment of CLD. Only one study, in which CLD was a key clinical outcome, met criteria for inclusion in the analysis. This double blinded, multicenter randomized trial compared inhaled beclomethasone in combination with salbutamol

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vs. beclomethasone alone. There were no statistically significant differences in mortality, CLD, need for parenteral dexamethasone, respiratory infections or positive blood cultures between the combination with salbutamol and beclomethasone alone. Furthermore there were no statistically significant differences in duration of ventilatory support, duration of oxygen supply or age of weaning from respiratory support (defined as assisted ventilation or oxygen supplementation) between the 2 treatment groups [10].

Inhaled prostacyclin (PGI2) has been administered to newborns with persistent pulmonary hypertension (PPHN) [9, 42, 65] and to infants with PPHN following surgical repair of congenital heart disease [11]. These studies showed improvement in oxygenation due to decrease of intrapulmonary shunt after treatment with aerosolized PGI2. Nevertheless these observations were never confirmed by subsequent large multicenter randomized trials.

The clinical trials summarized above provide no clear evidence of efficacy with aerosolized agents in the neonatal population. Furthermore different aerosol generators were used in these studies. It is important to remember that residual volumes vary among devices. Dubus et al reported residual volumes of 0.1 ml and 1.1 ml for vibrating mesh and jet nebulizer respectively [11]. Such factors as gas flows and different output rates could influence the emitted dose. Thus variations in device characteristics among studies make it difficult to provide objective comparison of clinical outcomes.

Type and location of the nebulizer

There are only a few options for aerosol entrainment within the ventilator circuit: 1) placement of the nebulizer within the inspiratory arm of the circuit or 2) introducing the aerosol between “Y” connector and patient interface. Connecting the nebulizer to the inspiratory arm via a “T” shape connector is recommended for metered dose inhalers (MDIs), vibrating mesh nebulizers and jet nebulizers. Entraining the aerosol between “Y” connector and patient interface is used mainly for MDIs with a holding chamber, although some recent studies have also suggested the utility of placement of vibrating mesh nebulizers in this location whenever a nebulizer with a low residual volume is used [12-14]. The general overview of clinically used aerosol generators, as well, as most critical variables influencing effectiveness of aerosolized formulations used for mechanically ventilated infants are included in table 1.

Table 1. Characteristics of different aerosol generators used for ventilated infants: ET – endotracheal, ‘Y’ – wye ventilator circuit connector, VHC – valve holding chamber. Adopted from [1]

<table>
<thead>
<tr>
<th>Principle of aerosol generation</th>
<th>Jet</th>
<th>Vibrating Mesh</th>
<th>Ultrasonic</th>
<th>MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas flow</td>
<td>active</td>
<td>passive</td>
<td>passive</td>
<td>passive</td>
</tr>
<tr>
<td>Location within circuit</td>
<td>inspiratory arm</td>
<td>inspiratory arm or between 'Y' and ET tube</td>
<td>inspiratory arm</td>
<td>inspiratory arm or between 'Y' and ET tube</td>
</tr>
<tr>
<td>Residual volume</td>
<td>large</td>
<td>small</td>
<td>small</td>
<td>VHC size</td>
</tr>
<tr>
<td>Aerosol particle size</td>
<td>depend on gas flow and formulation</td>
<td>depend on mesh and formulation</td>
<td>depend on formulation</td>
<td>depend on VHC size and type</td>
</tr>
<tr>
<td>Aerosol temperature</td>
<td>low</td>
<td>ambient</td>
<td>ambient</td>
<td>ambient</td>
</tr>
<tr>
<td>Efficacy expressed as inhaled dose % of nominal dose</td>
<td>lower</td>
<td>higher</td>
<td>mid</td>
<td>mid</td>
</tr>
</tbody>
</table>

Fok [2] compared different aerosol generators in delivering salbutamol labeled with technetium 99m (99mTc) to infants with bronchopulmonary dysplasia (BPD). The aerosols delivered to the infants by jet nebulization were significantly finer than those delivered by MDI (p = 0.005). Despite the larger particle size, the MDI was associated with significantly higher pulmonary deposition relative to the jet nebulizer, when results were expressed as a percentage of initial nebulizer reservoir activity (nominal dose) (0.19% vs. 0.08%, resp., p = 0.009) [2]. These data suggest that for intubated infants, smaller particle size at the aerosol generator does not insure superior pulmonary deposition and that type and location of the nebulizer may also influence the lung deposited dose [11] showed that the vibrating mesh nebulizer (Aeroneb Pro; Aerogen, Dungan, Ireland) was superior.
in pulmonary deposited dose when compared to jet nebulizer (MistyNeb; Airlife Inc., Montclair, CA), when both nebulizers were placed in the same location in the inspiratory arm of the ventilator circuit with a mass median aerodynamic diameter (MMAD) of 1.4 μm measured at the end of the ET tube [15]. This finding indicates that device characteristics such residual volume and output rate may drive clinical outcomes.

Based on Fok’s and Dubus’ findings, it appears that aerosol entrainment into the ventilator circuit is as important as particle size in lung deposition. In these studies, the jet and vibrating mesh nebulizers were placed within the inspiratory limb of the ventilator circuit, whereas the MDI was connected to the holding chamber placed between the “Y” connector and the ET tube [2]. Entraining the aerosol into the inspiratory arm of the circuit resulted in considerable dilution of the aerosol, because inspiratory flows were much lower than ventilator circuit flow rate especially when a jet nebulizer was used with an additional 6 l/min gas driving flow. Furthermore, the use of higher air-flows in the ventilator circuit can lead to the impaction of aerosol within the ventilator circuit before reaching the patient. It is also possible that very small particles (below 1 μm) generated by the jet nebulizer, (with relatively low inspiratory flows) were exhaled leading to reduced lung deposition [16].

Valved holding chambers (VHC) are used in order to optimize aerosol particle size generated by MDIs. The VHC allows time and distance for particle shrinkage and also acts as a large particle filter [17]. Removing the chamber may increase the impaction of aerosol within ET tube (up to 90% of the aerosolized dose) [18]. However, it is important to remember that placement of VHC, or even a “T” connector between the “Y” connector and patient interface, can increase ventilation dead space. Holding chambers can also be placed within the inspiratory arm of the ventilator circuit. Using a lung model, O’Doherty et al., demonstrated that such placement of the chamber increased aerosol delivery due to continuous filling of the chamber with aerosol during the exhalation phase of the breathing cycle, but had no effect on particle size [19]. It has also been shown that electrostatic charge can have a major influence on delivery of salbutamol generated by MDI [20]. However coating the plastic chamber with an ionic detergent solved the problem of electrostatic charge by the build up of a conducting layer on the chamber surface and improved aerosol delivery from plastic VHC [20]. Placement of the nebulizer closer to the patient (between the ET tube and “Y” connector) avoids potential dilution of the aerosol by the higher ventilator air-flow rates. Using a neonatal lung model, Turpeinen et al., demonstrated that placement of the nebulizer at the ET tube level improved drug delivery compared to in-line nebulizer placement within the inspiratory arm of the ventilator circuit [21]. Nevertheless, clinical studies with sodium cromoglycate did not show improvement in aerosol lung deposition (less than 1% of the nominal dose) with placement of the nebulizer closer to the patient [22]. Other studies have demonstrated enhanced lung deposition with placement of the nebulizer < 30 cm from “Y” connector within the inspiratory arm. This suggests that ventilator tubing can assume the function of an aerosol reservoir [19, 23].

In summary, if a MDI is used the VHC can be placed either in the inspiratory arm of the circuit or between “Y” and ET tube. If a jet or vibrating mesh nebulizer is used, they should be placed within inspiratory arm, nevertheless the exact location should be determined by well designed clinical studies; the ventilator setting should be adjusted if additional nebulizer driving gas flow is used. The vibrating mesh nebulizer results in superior lung deposition of the drug, most likely due to smaller residual volume and low operational gas flows.

**Particle size**

Recent studies of aerosol lung deposition in term and preterm infants have used an indirect method to assess lung deposition using a marker substance, sodium cromoglycate, which can be measured in the urine. Kohler et al., compared aerosol delivery to non-intubated spontaneously breathing infants using three different nebulizers: jet nebulizer (LC Star®; Pari, Starnberg, Germany), ultrasonic nebulizer (LS 290®; Systam, Villeneuve sur Lot, France), and ultrasonic nebulizer (Projet®; Artsana, Grandate, Italy). Although the LC Star had the highest lung deposition among the other nebulizers, only 0.89% of the nominal dose was deposited in the lungs after inhalation via LC Star [24]. This finding is supported by other studies on infants showing pulmonary deposition of less than 1% of the nominal dose for spontaneously breathing and mechanically ventilated patients [4, 25]. Significantly greater direct lung deposition was reported in an in vivo study done on intubated and mechanically ventilated macaques monkeys with the use of Aeroneb Pro and 99mTc diethylenetriamine pentaacetate. In this study, Dubus and colleagues reported aerosol with MMAD of 1.4 μm at the tip of the ET tube for both tested devices but 25 fold greater lung deposition of radiolabeled aerosol when generated by Aeroneb Pro synchronized with inspiration vs. Misty Neb in conti-
nuous mode (14% vs. 0.5% of the nominal dose respectively) [11]. These observations from clinical and nonclinical studies indicate that fine particle sizes that bypass artificial airways and upper airways can be effectively delivered into the lungs of ventilated patients, and that differences in residual volumes between nebulizers can drive deposition rates if they are expressed as percent of nominal dose. However, at the same time, small particles in combination with short inspiratory times and low inspiratory flows increase the risk for exhalation drug losses. Fok et al., demonstrated inferior lung deposition in infants with BPD treated with smaller aerosol particles (MMAD of 0.83 ± 0.01 μm) vs. larger aerosol particles (MMAD of 1.88 ± 0.01 μm) [2]. It has been shown that small particles (< 1 μm) are less dependent on gravitation and can be exhaled without deposition in the lungs. Calculations as well as actual measurements based on adult models have indicated that particles between 2-6 μm are deposited in central airways and above 6 μm are deposited in the oropharynx [26]. Studies evaluating particle size delivery to the upper airway of the preterm infants are limited. Minocchieri et al., using an upper airway model comparable to a 32-week gestation infant reported similar results. In this study the average MMAD of budesonide particles which passed upper airways was 1.6 μm [27]. However model-based studies do not account for amounts of exhaled drug; the results reflect only theoretical assumptions that should be supported by in vivo experiments.

O’Riordan et al., showed that the majority of the deposition within the tracheostomy tube occurred during the exhalation phase of the breathing cycle, suggesting that a significant fraction of inhaled aerosol was actually exhaled [16]. Intubated adults were mechanically ventilated and treated with saline labeled with 99mTc bound to human serum albumin. Aerosol was generated with jet nebulizer AeroTech II and entrained into the inspiratory arm of the ventilator circuit with settings selected to simulate a 4 kg infant with moderate to severe pulmonary disease. A jet nebulizer (Airlife™ Misty-Neb™ Baxter; Valencia, CA) was used in this study and was positioned in the inspiratory arm of the ventilator circuit. The study demonstrated that as the nebulizer air-flow increased, delivery to the lung model significantly decreased in a linear fashion; the mean percent delivery at 5 l/min was 4.8 ± 1.3% increasing the flow to 6.5 l/min significantly decreased the mean percent delivery to 3.7 ± 1.1%. Further increasing the flow to 8.0 l/min resulted in a significant decrease in the mean percent delivery to 2.7 ± 1.1% (p <0.015 vs. 5 l/min). This study also demonstrated higher aerosol deposition within the inspiratory arm of the ventilator circuit with higher air flows, which was most likely related to impaction [30]. A similar relationship between aerosol inhaled dose and ventilator bias flow was also reported by Ari et al [31]. Using a premature infant nose-throat model, Minocchieri et al., showed that higher aerosol flows lead to reduced lung deposition. There was a statistically significant decrease in aerosol delivery from 61.8 ± 5.3% to 26.0 ± 1.5% and 9.0 ± 0.8% of the nominal dose for 1, 5, and 10 l/min of inspiratory flow, respectively [32]. These in vitro studies have demonstrated that increased air flow presumably leads to increased aerosol impaction in the upper airways, resulting in decreased drug delivery and deposition in the lungs. Density is another gas condition, which may influence the effectiveness of inhalational therapy. Any gas density lower than air or oxygen can reduce air-flow turbulence through the narrow airways of the neonate. Fink et al., found that aerosol delivery via

In summary, for intubated and non-intubated infants who require breathing support, the most critical variable influencing particle size is patient interface. The particles should be small enough to bypass that interface with minimal impaction losses but should not be too small in order to avoid significant exhalation losses. It is important to remember that particle size is only one of many variables that can influence pulmonary drug deposition.

**Ventilation gas conditions**

Jet nebulizers use air-flow to generate the aerosol. Different commercially available jet nebulizers have different air flow parameters in order to optimize performance. Ultrasonic or mesh vibrating nebulizers need gas flow in order to entrain and carry aerosol towards the patient, although air flow is not required to generate the aerosol [29]. Coleman et al., tested different nebulizer air flows in combination with mechanical ventilation in a lung model with settings selected to simulate a 4 kg infant with moderate to severe pulmonary disease. A jet nebulizer (Airlife™ Misty-Neb™ Baxter; Valencia, CA) was used in this study and was positioned in the inspiratory arm of the ventilator circuit. The study demonstrated that as the nebulizer air-flow increased, delivery to the lung model significantly decreased in a linear fashion; the mean percent delivery at 5 l/min was 4.8 ± 1.3% increasing the flow to 6.5 l/min significantly decreased the mean percent delivery to 3.7 ± 1.1%. Further increasing the flow to 8.0 l/min resulted in a significant decrease in the mean percent delivery to 2.7 ± 1.1% (p <0.015 vs. 5 l/min). This study also demonstrated higher aerosol deposition within the inspiratory arm of the ventilator circuit with higher air flows, which was most likely related to impaction [30]. A similar relationship between aerosol inhaled dose and ventilator bias flow was also reported by Ari et al [31]. Using a premature infant nose-throat model, Minocchieri et al., showed that higher aerosol flows lead to reduced lung deposition. There was a statistically significant decrease in aerosol delivery from 61.8 ± 5.3% to 26.0 ± 1.5% and 9.0 ± 0.8% of the nominal dose for 1, 5, and 10 l/min of inspiratory flow, respectively [32]. These in vitro studies have demonstrated that increased air flow presumably leads to increased aerosol impaction in the upper airways, resulting in decreased drug delivery and deposition in the lungs. Density is another gas condition, which may influence the effectiveness of inhalational therapy. Any gas density lower than air or oxygen can reduce air-flow turbulence through the narrow airways of the neonate. Fink et al., found that aerosol delivery via
a MDI showed a linear increase when the gas density within the ventilator circuit was decreased [33]. The use of an 80% helium and 20% oxygen mixture in a dry ventilator circuit resulted in a 50% increase in the amount of drug delivered to the lower respiratory tract, compared with that observed with 100% oxygen (46.1% vs. 30.4%), respectively [34]. However, it is important to remember that air-flow based jet nebulizers may potentially exhibit decreased output rates when used with helium-oxygen mixtures [13]. Interestingly, non-invasive heliox ventilation has been recently shown to decrease resistive work of breathing and ventilator support requirements as well as improve gas exchange in premature infants [35].

Humidity is significant variable which potentially can influence the effectiveness of inhalational therapies. Standard of care ventilator support requires delivery of humidified and heated air to patients in order to avoid drying the airway mucosa [36, 37]. Several in vitro studies have investigated the relationship between humidification and aerosol lung deposition. Miller et al., using different jet nebulizers (AeroTech II®, CIS-US, Bedford, MA) and (Portex®, SIMS Portex, Inc., Fort Myers, FL) and 3 different ventilators designed for adults (with a driving flow of 8 l/min.) demonstrated that aerosol delivery increased nearly two-fold (\(p < 0.0001\)) by turning off and bypassing the humidifier. In addition, humidity increased the particle size at the tip of ET tube from 1.5 ± 0.1 μm to 2.3 ± 0.2 μm (\(p = 0.0006\)) by hygroscopic growth, suggesting greater particle impaction in the ventilator tubing [38]. Likewise, other studies showed an approximate 40% decrease in aerosol lung deposition when humidified and heated air was used [16, 39, 40]. Although studies were conducted under ventilated adult conditions, conclusions related to humidity are applicable to mechanically ventilated infants.

### Patient Interface

Patient interface can also act as a significant site of aerosol impaction. In an in vitro study, Ahrens et al., investigated the influence of different neonatal ET tube sizes and flows on aerosol deposition in a test lung. The results suggested that aerosol flows were more important than ET tube size on aerosol deposition of conventional aerosols in clinical use (MMAD = 3.95 μm). The study also showed that test lung deposition significantly improved when submicronic aerosol (MMAD = 0.54 μm) was delivered [41]. Crogan et al., showed that the percentage of aerosolized metaproterenol (Alupent®, Boehringer Ingelheim, Ingelheim, Germany) exiting the ET tube almost doubled for a 9.0 mm vs. 6.0 mm ET tube [42]. Everard and co-workers showed a drop in drug delivery when using a smaller ET tube (2.5 vs 3.0) during in vitro testing of Babylog Draeger neonatal ventilator circuit [43] and [11], reported that regardless of different aerosol particles at the nebulizers outlet, the particle size distribution at the end of the 3.0 mm ET tube was similar with an MMAD of 1.4 μm across all tested nebulizers [11].

As mentioned earlier these findings show that patient interface can be a critical variable determining the particle size delivered to a mechanically ventilated patient [11]. Unfortunately there are limited data on the influence of neonatal ET tube size on aerosol characteristics and lung deposition in in vivo studies.

### Summary

Inhalational therapy has not been proven to be effective for infants supported with mechanical ventilation in the phase III prospective clinical studies. Future trials of aerosolized medications should be appropriately designed in order to challenge all technical and physiological variables presented in this manuscript. Both, drugs as well as nebulizers and delivery systems should meet the needs and account for the physiological limitations of the smallest patients.

### References


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