Our greatest challenge: Aerosol-mediated drug delivery to premature and term infants

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Summary:

Aerosol-mediated drug delivery to the premature and term infant lung is consistently reported as achieving low levels of drug deposition. The variety of infant specific interventions and associated equipment available to the clinician mean that there is no consensus standard of care when it comes to aerosol therapy. The result is substantial variability in how aerosols are administered, and consequently, varying levels in the quality and success of therapy. The airway anatomy and respiratory physiology characteristic of these patients is manifested as low tidal volumes, rapid breathing rates, small bore airways and grossly, 'stiff' lungs. All these factors combine to reduce the opportunity for aerosol deposition. The opportunity for deposition in the lung is furthered reduced by means of the filtering effect of low bore tubing and interfaces and protective ventilatory strategies, *e.g.* bias flow and I:E ratios favouring greater exhalation times. However, despite these low levels of deposition, therapeutic levels of administration may still be achieved. A worked example for a 2 kg neonate is provided that details how, despite a 0.5 % lung dose, delivery on a μg/kg basis can exceed that of a 69 kg adult receiving a 10 % lung dose for the same course of treatment.

Introduction:

Aerosol-mediated drug delivery to premature and term infants has been proven feasible and well tolerated in the clinic. The key determinants of the efficiency of aerosol transport from the aerosol generator to the lung are generally well known in the adult setting, however, little is known about the factors at play in interventions specific to these patient groups.

The effect of bias flow, small bore tubing and interfaces compounded with the characteristic rapid breathing rates, low tidal volumes and unfavourable I:E ratios are associated with low levels of aerosol deposition in the infant lung. As a result of there being no consensus on the optimal setup for the administration of aerosols to infants, there is no established "standard of care" for aerosol therapy and so there is substantial variability in how aerosols are administered, and consequently varying levels in the quality and success of therapy.

Despite the small amounts of aerosol being delivered, minimum therapeutic dosing can nevertheless be achieved for pharmacologic agents. The poor efficiency of delivery however minimises the usefulness of aerosol-mediated delivery for other agents such as those with mechanical or surface active properties, for example, exogenous surfactants.

This abstract aims to give an overview of the difficulties in efficiently transporting aerosol to the premature and neonate lung, and also to present the current state of the art with respect to aerosol delivery across the various clinical interventions employed in the ventilatory support of these, the most fragile of patients.

Indications for aerosol-mediated drug delivery

Ventilatory support is a standard intervention in neonatal intensive care due to the high prevalence of respiratory conditions that present in this setting[1]. Examples include bronchiolitis and croup, Respiratory distress syndrome (RDS), post intubation respiratory failure, atelectasis, bacterial and fungal infections. In an effort to treat these conditions, a variety of agents have been delivered *via* aerosol. Refer to Table 1 for the classifications of drugs reportedly delivered to the lung in neonatal intensive care and the indications proposed for their use.

Aerosol-mediated delivery is not the go-to method of drug delivery worldwide. Whilst widespread across the US, the use of aerosols in neonate intensive care units (NICUs) in the rest of the world is not as common. A variety of

rationales are provided which include patient safety (for example the risk of volutrauma and barotrauma caused by mechanical ventilation) and what is thought to be the lack of appropriate receptors in the lung[2].

Drug Class	Examples	Proposed Indications
Bronchodilator	Adrenaline, Anticholinergics, β2-agonists	Bronchiolitis, Croup, Bronchospasm
Mucolytic	Hypertonic saline, Acetylcysteine	Atelectasis, mucus plug, ALI injury
Anti-infective	Antibiotic, Antifungal, Antiviral	Infection
Surfactants	Exogenous porcine, bovine or recombinant.	RDS, Merconium aspiration

Table 1: Some of the drug classes reportedly delivered to the lung in neonatal intensive care and the indications proposed for their use.

The neonate airway and lung as a conduit for aerosol

The human airways and lungs continue to mature for up to as many as 8 to10 years after birth. This manifests as several anatomical differences between infant and adult airways. Refer to Table 2 for a list of those of most relevance to aerosol delivery.

The Infant Airway *versus* the Adult Airway
Tongue larger relative to mouth size
Epiglottis larger, stiffer and angled more posteriorly
Shorter trachea
Narrow nares

Table 2: Some of the key differences between infant and adult airways that are of relevance to aerosol delivery.

Within the lungs, airway diameters increase over time, and the process of alveolization continues. At term birth, there are approximately 20-50 million alveoli formed in the lung and approximately 300 million by the age of 8. Concurrently, the alveolar surface area increases from 2.8 m^2 at term birth to 32 m^2 at 8 years of age and 100 m^2 by adulthood. This effectively translates to “treatable” area.

Mechanically, the infant lung has about one-twentieth of the compliance of an adult lung and a resistance about 15 times greater[3]. In combination with other factors, the result is short inspiratory times and fast breathing rates that limit the opportunity for aerosol deposition. It is thought that this phenomenon results in a greater fraction of the aerosol being exhaled than in other age groups[4].

As a further consequence of low compliance and high resistance, low tidal volumes (Vt) are all that are possible for spontaneously breathing infants and this must be considered by the care giver when setting the levels of ventilatory support. Tidal volumes of between 2.5 mL and 5 mL are on the lower end of those applied.

Clinical Interventions used in the provision of ventilatory support

Clinical interventions are either invasive or noninvasive in nature with noninvasive interventions the first choice in an attempt to reduce the burden of care, costs and adverse side effects. The equipment and circuitry unique to each intervention have a large bearing on the ultimate efficiency of aerosol delivery and hence are an important consideration if targeting aerosol to the lung.

The primary invasive intervention is mechanical ventilation *via* an endotracheal tube. Typically infants <27 weeks will be intubated as they can’t breathe spontaneously. Non-invasive interventions (NIV) include;

Bubble CPAP: The long-time standard of care. Infants > 27 weeks will receive CPAP to maintain continuous positive pressure during both inspiratory and expiratory phases when breathing spontaneously.

Low Flow Nasal Therapy: For Infants > 36 weeks low flow cannula up to 2L/min support a baby when CPAP is discontinued but the infant continues to have a minimal oxygen requirement.

High Flow Nasal Therapy: Infants >27 weeks will receive high flow therapy between 2-8L/min to provide a level of respiratory support similar to CPAP

Resuscitation: Used for ventilatory support for new-born infants during the period where other interventions are being set up.

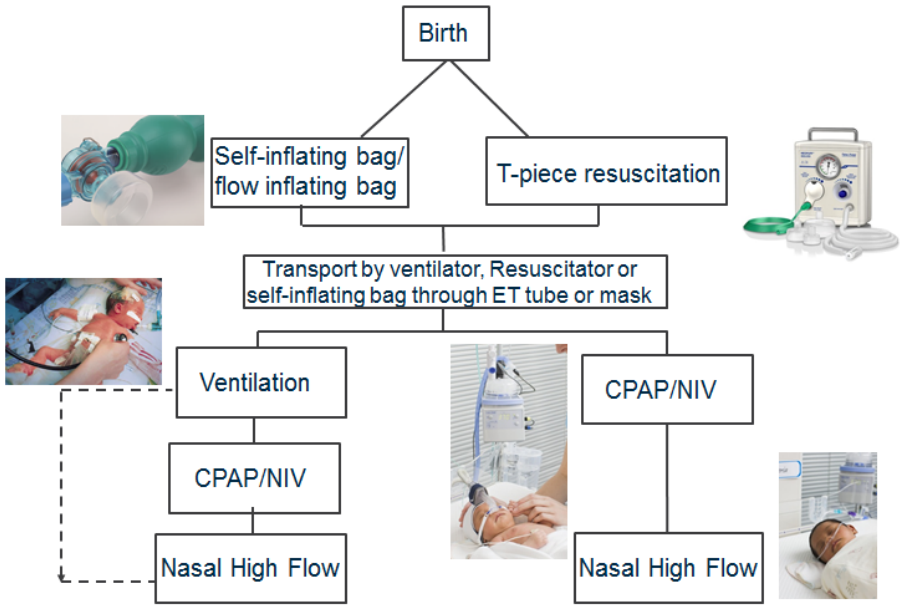

Figure 1: Potential progression of infant interventions in the provision of ventilatory support.

An example of current state of the art aerosol delivery to infants and what is possible

See Figure 2 for a scintigraphy image of lung deposition in a macaque using a jet nebuliser, the MistyNeb (Carefusion, San Diego, USA) and the Aeroneb Pro (Aerogen Limited, Galway Ireland).

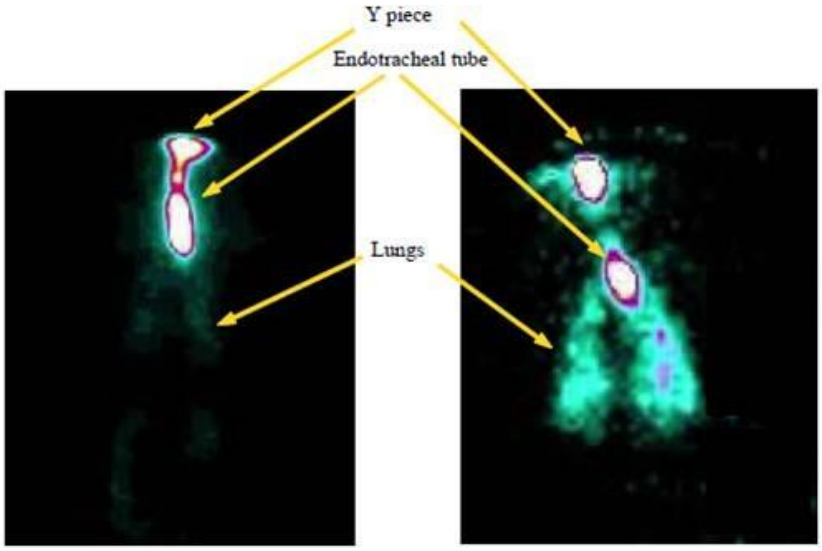

Figure 2: Lung deposition of 99mTc-DTPA in a mechanically ventilated neonate surrogate using a jet nebuliser (0.5 % of nominal dose) (left) and active vibrating mesh nebuliser (12.6 % of nominal dose) (right).

Until relatively recently, deposition rates in the order of 0.5 to 2.7 % of the nominal dose were the maximum reported in the literature[5]. With the development of passive aerosol generators such as the actively vibrating mesh nebulisers, aerosol deposition rates in *in vivo* neonate surrogates has been reported to be as high as 12.6 %[6].

Despite these low deposition rates, the potential to deliver the minimum therapeutic dose to the patient is still possible, as demonstrated in Table 3.

Patient	Nominal dose (μg)	Respirable dose (%)	Lung dose (μg)	μg/kg dose
Adult (69kg)	2500	10	250	3.60
Neonate (2kg)	2500	0.5	12.5	6.25

Table 3: Worked example of mg/kg aerosol dosing levels in both an adult and neonate patient.

In the above example the same dose of drug was placed into the same jet nebuliser type and both patients intubated and mechanically ventilated. Both patients received drug, however, the adult patient received as much as 20 times the respirable dose. Considering the concentration of the nominal dose, there was an even greater difference in lung dose (250 *versus* 12.5 μg). However, when considering the weight of the patient, the neonate patient is seen to receive a greater mg/kg dose than the adult (6.25 *versus* 3.60 μg/kg).

Whilst the majority of therapeutics have a pharmacologic effect, and as such may easily attain a therapeutic effect based on the μg/kg delivery rates, some therapeutics including exogenous pulmonary surfactants have a mechanical effect and require an absolute minimum amount to be delivered to the lung to be effective (pulmonary surfactants are surface active and serve to reduce the surface tension within the lung, allowing for ease of inflation and deflation during breathing). Such therapeutics will require the development of high efficiency aerosol delivery systems.

References

1. Darlow BA, Mogridge N, Horwood LJ, Wynn-Williams MB, Austin NC. "Admission of all gestations to a regional neonatal unit versus controls: neonatal morbidity." *Journal of paediatrics and child health*45.4 (2009): 181-186.
2. Chavasse R, Seddon P, Bara A, McKean M. "Short acting beta2-agonists for recurrent wheeze in children under two years of age." *Cochrane Database Syst Rev* 2 (2002).
3. Lumb, A. B. "Nunn's Applied Respiratory Physiology. 2005." Chapter 14.
4. Ehtezazi, Touraj, and A. Turner. "The Application of Mechanical Aerosol Delivery Systems in an in vitro Model of Mechanically Ventilated Neonates."*Recent patents on drug delivery & formulation* 7.3 (2013): 174-183.
5. Fink J. Aerosol delivery to ventilated infant and pediatric patients. Resp Care. June 2004. Vol 49, No. 6.
6. Dubus JC1, Vecellio L, De Monte M, Fink JB, Grimbert D, Montharu J, Valat C, Behan N, Diot P. In Vitro / In Vivo Comparison of Lung Deposition of 99mTc-DTPA in a Model of Mechanical Ventilation in Infants. American Thoracic Society International Conference (ATS), May 2003