Clinical Controversies in Pediatric Aerosolized Drug Delivery

Rob DiBlasi RRT-NPS, FAARC
Research/QI Manager, Respiratory Care
Principle Investigator
Seattle Children's Hospital

Disclosures

- Received funding from Mallinckrodt Medical (Ikaria) and Draeger Medical for research and speaking
- Received research funding from United Therapeutics
- Received research funding from Aerogen Pharma to study aerosolized surfactant delivery in rabbits

Clinical Controversies in Pediatrics

- Blow-by versus mask vs mouthpiece
- pMDI with Spacer vs SVN
- BAN vs continuous nebulizer therapy
- Aerosolization with Noninvasive Ventilation
  - Single limb circuit, HFNC, Bubble, Fluidic-flip, etc.
- Defining optimal circuit position for nebulizer during invasive mechanical ventilation
- Drug delivery in HFOV
- Nebulization of exogenous lung surfactant

Clinical Controversies in Pediatrics

Research

- Parents are less willing to expose their children to radiation
- As RTs, we rely heavily on studies *in-vitro*
- We extrapolate from previous studies and expect that devices will work with ALL treatment delivery options

Aerosol Delivery in Small Infants

- Aerosol drug particles are lost in the upper airway (high deadspace)
- Pulmonary deposition of aerosol particles
  - "Itty bitty" airways
  - ↑ resistance
  - Low Vt and FRC
- Residence time for aerosolized medication particles
  - Short respiratory cycle times (low I:E)
- Ideal aerosol drug particle size: 1-5 µm

<3% of the nominal dose in infants and 10-58% in adults
Aerosol delivery in non-intubated spontaneously breathing infants and children

| Reference | No. of Patients | Type of Patients | Aerosol Device | Deposition (%)
|-----------|-----------------|-----------------|----------------|-----------------|
| Selnes et al. | 9 | Italian (S, F, J) | Nebulizer to 1425 mL spacer | 0-0.13
| Choe et al. | 11 | Italian (6 F, 5 M) | Nebulizer | 0.9-1.3
| Clow et al. | 8 | Children (≤ 3 yr) | Nebulizer | 1.4-4
| Dwork et al. | 20 | Italian | Nebulizer | 6.16-1.3
| Aykan et al. | 24 | Italian | Nebulizer | 1.3-1.9
| Todd et al. | 11 | Children (≤ 4 yr) | SDE with spacer | 19.1
| Willamsette et al. | 17 | Children (≤ 4 yr) | Nebulizer to MDI with spacer | 1.4-1.1

Similar aerosol studies in adults have shown 8-22% lung deposition.

Delivery Options

- Devices
  - pMDI with spacer
  - Jet
  - Ultrasonic
  - Vibrating mesh
- Delivery Options
  - Spontaneous breathing
  - Bagging through ET-tube
  - In-line during MV and NIV

“The most effective method for aerosol drug delivery remains an elusive practice”

DiBlasi. Extremely rare personal communication, circa. 2009
What device and when…

- Explore published data related to delivery device efficiency
- Consider the respiratory support device that the drug is being delivered with
- Ability for the patient to tolerate and coordinate respiratory effort with drug delivery
- Patient preference
- Cost

<table>
<thead>
<tr>
<th>Aerosol Device and Interface</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small-volume nebulizer with mask or hood</td>
<td>Infants</td>
</tr>
<tr>
<td>Small-volume nebulizer with mask</td>
<td>≤ 3 y</td>
</tr>
<tr>
<td>Small-volume nebulizer with mouthpiece</td>
<td>≥ 3 y</td>
</tr>
<tr>
<td>pMDI with valved holding chamber/spacer and mask</td>
<td>&lt; 4 y</td>
</tr>
<tr>
<td>pMDI with valved holding chamber/spacer</td>
<td>≥ 4 y</td>
</tr>
<tr>
<td>DPI</td>
<td>≥ 4 y</td>
</tr>
<tr>
<td>MDI</td>
<td>≥ 5 y</td>
</tr>
<tr>
<td>Breath-actuated MDI (eg. Autohaler)</td>
<td>≥ 5 y</td>
</tr>
<tr>
<td>Breath-actuated nebulizer</td>
<td>≥ 5 y</td>
</tr>
</tbody>
</table>

pMDI = pressurized metered-dose inhaler
DPI = dry powder inhaler

Guidelines for SVN

- Follow manufacturer specifications for use
- Sit em’ up
- Encourage deep breathing
- Don’t tap the neb when it sputters
- Encourage mouthpiece if possible

Guidelines for SVN

- Takes about 10-15 mins
- It is preferred that the treatment be taken with a mouthpiece (≥ 3 years old)
  - Tough to coordinate
  - Obligate nasal breathers
- Mask works but not as well as mouthpiece
  - Mask should be tight-fitting, low dead space

Nebulizer performance

Hardy JG et al. Respiratory Medicine, 1993

Keep things interesting
**Clinical Controversy #1**

“The best way to give pediatric aerosol therapy to and infant is when they are crying because they are taking large breaths”

![Graph showing aerosol delivery to a sleeping infant](image)

**Clinical Controversy #2**

“Blow-by aerosol treatments are better tolerated and result in better drug delivery than a facemask”

![Facemask and Aerosol Delivery In Vivo](image)

![Video of Baby Ava using a Nebulizer for Bronchitis](image)

![Diagram showing blow-by vs. facemask](image)
Aerosol Delivery Alternatives for Infants

- Infants that are incapable of tolerating a mask treatment may also benefit from aerosol delivery by an infant hood
  - May be less likely to make the infant cry
- Amirav et al. compared radiolabeled bronchodilator delivery in 14 wheezy infants between a jet nebulizer with an aerosol mask and the same jet nebulizer attached to a clear plastic infant hood
  - Drug delivery was similar with mean lung drug deposition of 2.6% and 2.4% with the hood and mask, respectively.

Clinical controversy #3

“The best way to administer a bronchodilator is with a small volume neb because pediatrics can’t coordinate with a pMDI/VHC”

Perceived Limitations

- pMDI/VHC
  - Poor efficiency
  - Not well tolerated because they cannot open the demand valve
  - Tidal volumes are too small to clear the chamber of medication
  - Expensive
- SVN
  - Poor overall efficiency (2% to 8%)
  - All nebulizer’s are not equivalent
  - Loss on exhalation
  - Loss with residual volume
  - Loss with tubing
  - Loss with poor mask fit

AeroChamber MAX™ VHC

Are all Chambers Created Equal?

Nebulizers vs Metered Dose Inhalers with AeroChamber® VHC and Mask in Children 2 to 24 Months

- MDI with AeroChamber® VHC
  - As clinically effective as nebulizer
  - Less side effects
  - Reduced admissions
  - Efficient and easier method of aerosol delivery

Clinical Efficacy Studies of SVN vs. pMDI+VHC
Acute Asthma

- William JR. ’96
  - 60 children 6-18 years in ED with acute asthma
  - PARI-JET II vs. Aerochamber vs. ACE
  - Outcome measures changes in PEFR and RR
  - No difference between delivery methods
  - pMDI + VHC more cost effective

- Schuh S. ’99
  - 90 children 5-17 years in ED, outcome FEV<sub>1</sub>
  - pMDI + Aerochamber (high & low dose) vs. SVN
  - No difference between groups, ↑HR with SVN

Valved Holding Chambers versus Nebulizers for beta-agonist treatment of acute asthma?

- 2001 analyzed 1076 children and 444 adults who were included in 22 trials.
- MDI’s with holding chambers produced outcomes that were at least equivalent to those of nebulizer delivery.
- In children with acute asthma, holding chambers have advantages compared with nebulizers.

Cates CJ, Rowe B, Bara A. 2003 Cochrane Review

B-Agonists Through MDI/VHC vs Nebulizer Children
Under 5 Years of Age
With Moderate to Severe Asthma in the ED
A Systematic Review with Meta-Analysis

- MDI/VHC more effective in:
  - Decreasing Hospitalization
  - Improving Clinical Asthma Score


Costs of Albuterol Administration

<table>
<thead>
<tr>
<th></th>
<th>Jan-May 2004</th>
<th>Jan-May 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Txs</td>
<td># Pts</td>
</tr>
<tr>
<td>MDI-VHC</td>
<td>2,474</td>
<td>197</td>
</tr>
<tr>
<td>SVN</td>
<td>7,441</td>
<td>714</td>
</tr>
</tbody>
</table>

Device Costs

- SVN-mask $2.36 ea X 3 = $7.08 x (#Pts) $5,055 $2,089
- Multi-doseivial $1.94 x (#Pts) $1,385 $572
- MDI canister $2.45 ea x (#Pts) $483 $982
- VHC $13.65 x (#Pts) $2,689 $5,474

Labor Costs

- MDI-VHC = 13.2 x 0.61 = $8.05 x (#Txs) $19,916 $49,733
- SVN = 20.4 x 0.61 = $12.44 x (#Txs) $92,566 $22,927
- Total Tx costs $122,094 $81,777
- Total # Txs 9,915 8,021
- Total cost per Tx $12.31 $10.20

Percent cost reduction 04 to 06 = 21%

Clinical Controversy #4
“Continuous Nebulization of bronchodilators has been used for decades in the ER and other devices cannot deliver as much drug”
Continuous Nebulization


- 30 children; (aged 2-18 years)
  - Used 70/30 vs 100% to drive continuous nebulizer
  - PI Score was lower with Heliox than 100% (P<0.05)
  - Heliox group was discharged earlier

**In-Vitro Comparison of 4 Large-Volume Nebulizers in 8 Hours of Continuous Nebulization.** Berlinski A et al., Respir Care

- No differences; Misty Finity and Hope nebulizers had more consistent delivery

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Breath Actuated Nebulizers

**Randomized Controlled Trial of a Breath-Actuated Nebulizer in Pediatric Asthma Patients in the Emergency Department**

Sabato et al., Respiratory Care 2011

- Greater improvement in clinical asthma scores
- Lower admission rate

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**Clinical Controversy #5**

“All patients must be taken off of noninvasive respiratory support to receive a nebulizer treatment”

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Perhaps the only consensus about mechanical ventilation of infants is that, all else being equal, avoidance of mechanical ventilation is the best way to avoid lung injury.

Aerosol Drug Delivery During Noninvasive Support

- Aerosols are frequently administered to neonatal patients to:
  - Alleviate bronchospasm
  - Reduce airway inflammation
  - Facilitate mucus clearance
  - Improve pulmonary blood flow
  - Treat infection
  - Improve compliance

- Many of these aerosols are not given with noninvasive support:
  - Gas powered nebulizers may increase tidal volume, pressure, and triggering
  - Presumed safety hazards and poor deposition
  - Many patients are either kept on a ventilator or removed from noninvasive ventilation for treatments

Diseases That May Require Inhaled Drugs During Noninvasive Support

<table>
<thead>
<tr>
<th>Neonatal Lung Disease</th>
<th>Inhaled Specialty Gases</th>
<th>Inhaled Aerosols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Distress Syndrome</td>
<td>NO and Heliox</td>
<td>Inhaled Surfactant: Preferred (experimental)</td>
</tr>
<tr>
<td>Meconium Aspiration Syndrome</td>
<td>NO and Heliox</td>
<td>Inhaled Prostacyclins: Iloprost, Treprostinil, and Flolan; PFC: Experimental</td>
</tr>
<tr>
<td>Congenital Diaphragmatic Hernia</td>
<td>NO</td>
<td>PFC: Experimental</td>
</tr>
<tr>
<td>Primary Pulmonary Hypertension</td>
<td>NO</td>
<td>Prostacyclins: Iloprost, Treprostinil, and Flolan; PFC: Experimental</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>NO</td>
<td>Antibiotics, Hypertonic Saline</td>
</tr>
<tr>
<td>Bronchopulmonary Dysplasia</td>
<td>NO</td>
<td>Corticosteroids and Bronchodilators</td>
</tr>
<tr>
<td>Congenital Cardiac Anomalies</td>
<td>NO</td>
<td>Prostacyclins: Iloprost, Treprostinil, and Flolan; PFC: Experimental</td>
</tr>
</tbody>
</table>

Aerosol Delivery with High Flow Nasal Cannula

<table>
<thead>
<tr>
<th>GASFLOW</th>
<th>3 LPM</th>
<th>6 LPM</th>
<th>p-values between Flows Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heliox (80%)</td>
<td>1.14 ± 1.54</td>
<td>1.42 ± 0.54</td>
<td>p=0.028</td>
</tr>
<tr>
<td>Oxygen (100%)</td>
<td>10.55 ± 0.21</td>
<td>11.95 ± 0.50</td>
<td>p=0.092</td>
</tr>
<tr>
<td>p-values between Heliox and Oxygen</td>
<td>0.043</td>
<td>0.041</td>
<td></td>
</tr>
</tbody>
</table>

Vt – 100 mL
RR – 30 BPM

Aerosol Delivery with High Flow Nasal Cannula with Adult Cannula

<table>
<thead>
<tr>
<th>GASFLOW</th>
<th>10 lpm</th>
<th>30 lpm</th>
<th>50 lpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>O2</td>
<td>27.1%</td>
<td>12.03%</td>
<td>3.6%</td>
</tr>
<tr>
<td>80% Heliox</td>
<td>27.9%</td>
<td>14.4%</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

Nasal High Flow Nebulization

TABLE 1—Aerosol Lung Deposition

<table>
<thead>
<tr>
<th>Control conditions</th>
<th>Jet nebulization</th>
<th>Vibrating mesh nebulization</th>
<th>Aerosol face mask jet nebulization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mass on nasal mucosa model</td>
<td>0.012 ± 0.004</td>
<td>0.012 ± 0.004</td>
<td>0.012 ± 0.004</td>
</tr>
<tr>
<td>On top of the NIF circuit</td>
<td>0.012 ± 0.004</td>
<td>0.012 ± 0.004</td>
<td>0.012 ± 0.004</td>
</tr>
<tr>
<td>Total mass on nasal mucosa model</td>
<td>0.012 ± 0.004</td>
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</tr>
</tbody>
</table>

Reminiac et al., Pediatric Pulmonary, 2016
HFNC Aerosol Drug Delivery

**Setting:** Aerosol research laboratory.

**Measurements and Main Results:** The inspired dose (percent of nominal dose) for each cannula size and flow rate was 2.5%, 0.8%, 0.4%, and 0.2% for the adult cannula at 5, 10, 20, and 40 L/min respectively; 1.2%, 0.6%, 0.1%, and 0.0% for the pediatric cannula at 3, 5, 10, and 20 L/min respectively; and 0.6%, 0.6%, and 0.5% for the infant cannula at 3, 5, and 8 L/min respectively. Most (62–80%) of the loaded albuterol dose accumulated within the adaptor. For each cannula size, there was a significant decrease in deposition with increasing flow rate.

The Vapotherm 2000i system uses comparatively smaller diameter tubing and prongs compared to the F&P system.

Perry AS et al., PCCM, 2013

Infant Nasal Continuous Positive Airway Pressure (NCPAP) and NIV

- Infants may require intermittent aerosolized medication delivery with nasal CPAP or NIMV.
- Sunbul et al. showed fluidic flip CPAP (SiPAP) provided lower drug mass than HHFNC (P=0.003) and bubble CPAP (P=0.008).
- There were no differences between the nebulizer circuit positions for HHFNC (P=0.43) and SiPAP (P=0.13) but during B-CPAP nebulizer placement at the humidifier provided greater drug delivery than when placed proximal to the patient (P=0.007).
- Farney et al. showed greater delivery of technetium-99m-labeled diethylene triamine penta-acetic acid via VM nebulizer placed 32 cm from nasal CPAP prongs than when placed back at the humidifier (21 ± 11% vs 0.3 ± 0.4%, respectively, P < .001) during simulated neonatal CPAP (Infant Flow SiPAP (CPAP setting), Carefusion, San Diego CA).
- Placing the nebulizer close to the humidifier resulted in 59 ± 8% of the aerosol being deposited in the inhalation tubing along the heater wire and <0.5% to the lung model.

Sunbull FS et al., Peds Pulm, 2014
Farney KD et al., Resp Care, 2014

Safety Related to Aerosol Delivery During Noninvasive Support

- Larger infants are being supported with NIV.
- Therapy doesn’t need to be stopped!
- In humans, aerosol drug delivery during NIV is 30% greater than when no NIV is used.
- The nebulizer should always be placed as close as possible to the patient and after the expiratory leak valve.
- Efforts should be made to minimize excessive leak (chinstrap or full facemask) to provide optimal aerosol drug delivery during NIV.

DiBiase et al., Resp Care, 2010

Infant Nasal Continuous Positive Airway Pressure (NCPAP): Aerosol Delivery

Farney KD et al., Resp Care, 2014
Recommendations for Aerosol Drug Delivery with a Vibrating Mesh Nebulizer During Noninvasive Support

Form of Noninvasive Support | Reported Deposition (% nominal dose) | Suggested Nebulizer Location | Safety Concerns | Other
---|---|---|---|---
HFNC | 0.5-1.3 | Prior to the humidifier or proximal to patient airway interface; should not use ultrasonic | Less deposition than a mask treatment but may be better tolerated, infants may help deposition | 
Fluidig®-Neb and iGAP | 0.79-20 | Proximal to patient airway interface | Fluid accumulation in pressure generated high frequency ventilation | 
Bubble NCPAP | 1-24 | Prior to humidifier and integrated into patient circuit, delivered with flow limitation | Fluid accumulation in expiratory limb and excessive CPAP levels | 
Ventilator NCPAP and IMV | 0.7-12.6 | Proximal to patient airway interface | Has not been evaluated noninvasively | 
BiPAP (larger infants) | 1.2-10 | Integrated into mask (NIVO) or as close to patient as possible | High inspiration too much drug delivered to airway | 
Nasal HFV | ~30 | Proximal to patient Y; between ET tube | High deposition; too much drug delivered to airway | 

Based on invasive studies with ET tube.

Technical aspects with drug delivery

Medication Delivery
- Device choice
- Delivery options
- Humidification
- Breathing and gas flow patterns
- Configuration of the ventilator circuit
- Size and condition of ETT

Patient Safety
- Settings adjustments
- Deadspace
- Imposed resistance
- Lung-injury
- Destabilization
- Infection

Clinical Controversy #6
“Vibrating mesh, gas powered SVN and pMDI/spacer provide similar drug delivery in intubated pediatrics”

Are pMDIs and spacers more effective than nebulizers in intubated infants?

- Spontaneous breathing infants (facemask):
  - There were no significant differences in % lung deposition between pMDI/spacer (0.67 ± 0.17) and nebulizer (0.28 ± 0.01)

- Intubated/mechanically ventilated
  - % lung deposition from the pMDI/spacer was greater than nebulizer (0.98 ± 0.19 vs 0.22 ± 0.08 vs P = 0.009)
  - There was huge inter-subject variability in lung deposition
  - Aerosol had a tendency to be distributed in the central airways

Fok et al. Pediatric Pulmonology. 1996

Vibrating Mesh Nebulizer Compared With Metered-Dose Inhaler in Mechanically Ventilated Subjects

Meagan N Duhosky MSc RRT, Yi-Fu Chow MD, Mary E Heiniken MSc RRT, and David L Yonces MHS FAARC

BACKGROUND: The impact of various aerosol delivery devices on patient outcomes during mechanical ventilation is unknown. Few studies of drug delivery in higher ventilator associated pneumonia (VAP) rates than another, multiple patient outcomes may be affected. This study aimed to determine whether there was a difference in VAP occurrence and patient outcomes days receiving ventilation and hospital mortality between the vibrating mesh nebulizer (InSpace) and the meter-dose inhaler (MDI), 100% HFV. This retrospective study reviewed medical records for all mechanically ventilated, adult patients with an order for aerosol treatment from August 2011 to August 2013. The hospital converted from NIOB to vibrating mesh nebulizer in August 2012, and data were gathered from prior to the new conversion. Excluded were patients with a tracheostomy, patients who were mechanically ventilated for <12h, patients who received a combination of nebulizer and MDI treatments, or patients who were using a MDI for a different indication. The results were: 1) VAP was lower in patients who received the vibrating mesh nebulizer (InSpace) compared to the MDI (22% vs 28%, P = 0.003); 2) hospital mortality was higher in the MDI group (29% vs 11%, P = 0.003); and 3) the cost was lower in the Vibrating mesh group compared to the MDI group ($150 vs $250). Treatment Modality | Pediatric Patient Simulation (µg Actuation) | Mean ± S.D.
---|---|---
NEO-P | 3.3 ± 1.2 | 3.8 ± 2.1 | CH-S
MV | 5.5 ± 0.3 | 10.7 ± 0.9 | 10.0 ± 1.1
MR | 6.0 ± 1.0 | 10.5 ± 0.7 | 12.1 ± 1.8
DiBlasi et al., Respiratory Care 2010

A Novel, Versatile Valved Holding Chamber for Delivering Inhaled Medications to Neonates and Small Children: Laboratory Simulation of Delivery Options
Robert M DiBlasi RRT-NPS, Dominic P Congia RRT MLA FAARC, Mark W Nagel, Cathy C Doyle, Valentina I Arvelackova, Robert S Al, and Mylo P Mitchell PhD Chest CT
Clinical Controversy #7
“The nebulizer position has no effect on drug delivery but should be placed back at humidifier in all pediatric patients”


With Bias Flow
VM and JN more Efficient Placed
Prior to Humidifier
As Bias flow Increases
deposition decreases
VM > JN


Illoprost drug delivery during infant conventional and high-frequency oscillatory ventilation

Robert M. DiBiasi,1,2 Dave N. Crosett,1, Shujie Shen,1, Jie Zhang,1, James B. Fink,1, Delphine Yang1

Job Aid: Evidence Based Nebulizer Compatibility and Configuration for Noninvasive and Invasive Ventilation

Description
Guideline children in hospital have received many new nebulized pediatric inhaled and invasive respiratory support devices. It is unclear what type of pediatric nebulizer is best for use in pediatrics and which is the most efficient in delivering the drug. Advances in aerosol research have addressed many of these safety concerns and quantified drug delivery using these devices. This job aid serves as an addition to the Continuous Nebulizer of Medications job aid that is provided on CHILD and includes ALL forms of support used at SCH by the RT department.

Nebulizer Selection
1. In pediatric pulmonary nebulizer, patients of infants and young children for inhaled drug delivery. Inhaled drug delivery in infants and young children for inhaled drug delivery. This recommendation is intended for use in pediatric patients, not adults.
2. In non pediatric patients, a nebulizer may be used with a nebulizer ventilator but not in patients 12 kg and with 
3. In non pediatric patients, a nebulizer may be used with a nebulizer ventilator but not in patients 12 kg and with 
4. In non pediatric patients, a nebulizer may be used with a nebulizer ventilator but not in patients 12 kg and with 
5. In non pediatric patients, a nebulizer may be used with a nebulizer ventilator but not in patients 12 kg and with 

References
Berlinski, A. Resp Care 2013

Clinical Controversy #8

“Drug cannot be delivered during HFOV because of short inspiratory times, small tidal volumes, and inertial impaction which reduces aerosol delivery to the lung”

Clinical Controversy #9

“Aerosolized surfactant will never be feasible in infants with respiratory distress”

Background: Surfactant Delivery

- Direct tracheal instillation of surfactant has been shown to reduce mortality and morbidity in infants with RDS
- Surfactant replacement incorporates liquid bolus instillation via endotracheal tube (ETT) or catheter
- Requires short-term invasive positive pressure ventilation (PPV) and monitoring which may lead to complications in pre-term infants:
  - Invasive PPV (injury/inflammation), short-term tracheal or bronchial obstruction, hemodynamic instability, pulmonary hemorrhage, hyperventilation, neurologic sequelae
**Background**

- Aerosolized surfactant with invasive ventilation
  - Potentially better distribution of drug to distal airways and fewer complications than liquid bolus instillation
- Aerosolized surfactant combined with noninvasive support (CPAP)
  - May reduce need for invasive mechanical ventilation and complications related to intubation and ventilation
- Nebulized surfactant in animal models improved pulmonary mechanics, lung structure integrity, and reduced lung inflammation, even with minimal deposition in the lungs [Lewis 1991; Lewis 1993; Wolfson 2008]
  - One study in animals did not show improved pulmonary parameters with relatively larger aerosol doses than instilled surfactant [Fok 1998]
  - <2% lung deposition with ultrasonic and jet nebs

**Challenges in Aerosolized Surfactant Delivery**

- Inefficiency of gas powered nebs
- Drug loss due to continuous nebulization during respiratory cycle
- Inability to sufficiently provide drug prior to onset of inhalation
- Frequently require 3-4 x dose used with direct instillation
- Low drug deposition in infants (<3%)
- May create deadspace
- Nebulizers may become clogged and inoperable or degradation of aerosol
- May impact triggering, PEEP, and tidal volume

<table>
<thead>
<tr>
<th>Aerosol Characteristics</th>
<th>CVM</th>
<th>PDAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL₅₀ (a.k.a. VMD)</td>
<td>3.5 micron</td>
<td>1.05 micron</td>
</tr>
<tr>
<td>GSD</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Output Rate</td>
<td>0.05 mL/min</td>
<td>0.33 mL/min</td>
</tr>
</tbody>
</table>

**Advances in Aerosolized Drug Delivery in Noninvasive Support**

- Standard vibrating mesh and photo defined aperture plate wafer (Courtesy of Aerogen Pharma)
- Particle size distribution and output rate of 1:1 diluted surfactant with CVM and undiluted surfactant solution with PDAP

**Preclinical Prototypes**

- ACAD Software
- ACAD Hardware
- Airflow Sensor
- Ventilator

<table>
<thead>
<tr>
<th>Aerosol Characteristics</th>
<th>CVM (1:1)</th>
<th>PDAP (undiluted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL₅₀ (a.k.a. VMD)</td>
<td>3.5 micron</td>
<td>1.05 micron</td>
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<tr>
<td>GSD</td>
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<td>1.9</td>
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<td>0.33 mL/min</td>
</tr>
</tbody>
</table>

**Synchronisation Of Aerosol With Breath**

-Courtesy Aerogen Pharma

**Hypothesis**

- We hypothesized similar gas exchange, mechanics, WOB, lung recruitment and safety effects with direct surfactant instillation and aerosolization with a novel breath-synchronized vibrating mesh nebulizer (VMN) with the same surfactant dose
- Alveofact 108 mg/kg (3-4 mL) instillation via ETT (n=5) or aerosol with a breath-synchronized VMN (n=5)
Methods

- New Zealand rabbits (1.55 ± 0.19 kg) were sedated, anesthetized, intubated, with 0.9% saline lavage washout to PaO\textsubscript{2} < 75 torr on FiO\textsubscript{2} 0.5
- Assist-Control Volume Guarantee ventilation
- Instrumented with arterial, jugular and Pes catheter (WOB)
- Gas exchange and ventilation parameters were recorded every 30 minutes for 3 h post administration
- Unpaired T-test was used to compare (mean±SD) differences in physiologic outcomes at each interval; P<0.05 was significant
- Animals were sacrificed and static pressure-volume curves were obtained

![Graphs and charts illustrating dynamic compliance, respiratory rate, peak inspiratory pressure, and ventilation efficiency index.](Image URL)

Oxygenation Index

![Graphs and charts illustrating oxygenation index.](Image URL)

Ventilation Efficiency Index

![Graph showing ventilation efficiency index.](Image URL)

Direct Instillation (Catheter)

Inspiratory Impedance

Aerosolization (VM Nebulizer)

Relative Change in End-Expiratory Lung Volume from Baseline (post-lavage)

Relative Change in Inspiratory Lung Volume from Baseline (post-lavage)
Preliminary Data: Surfactant-Deficient Rabbits - nCPAP and Aerosolized Surf/ nCPAP

<table>
<thead>
<tr>
<th>Time</th>
<th>Control (No Surfactant)</th>
<th>50 mg Aerosolized Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre Lavage</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Post Lavage</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0.5 hr Post Extubation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CPAP</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1.0 hr Post Extubation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CPAP</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1.5 hr Post Extubation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CPAP</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2.0 hr Post Extubation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CPAP</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2.5 hr Post Extubation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CPAP</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3.0 hr Post Extubation</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CPAP</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Discussion/Next Steps

• Previous study showed despite using 4-fold greater dose with aerosolized surf./CPAP, there were no differences in outcomes in piglets supported with CPAP following direct instill. (Lampland 2014)
• (Re)intubation is 40-50% in pre-term infants, even with InSurE strategy and even higher when early CPAP used
• Nearly 1M pre-term newborns die each year worldwide
  • Lack of ventilators and surf.

Clinical Research: Surf/CPAP

• AEROSURF® KL₄ (Lucinactant) delivery with ADS
  • Unique capillary aerosol generator (CAG) technology utilizing pressure and heated capillary demonstrated ability to break through the barrier to effectively aerosolize KL₄ surfactant
  • Continuous, not breath synchronized: 1 to 3μm range

Pediatric Aerosol Controversies

• Drug deposition <0.35% when an infant is crying or screaming
• Negligible drug is delivered with BB neb (0.3%), even when infant is calm
• Drug delivery is 5 fold greater in a sleeping or calm infant; may consider infant hood
• Aerosolized drugs can be delivered with most forms of noninvasive support
• The days of continuous nebulizers are almost outnumbered
• pMDI/spacers are equally effective to SVN in intubated and non-intubated pts. but VM needs to be explored
• Nebulizer position matters in pediatrics but may not in adults
• Drug delivery is increased with HFOV over conventional
• Aerosolized surfactant for noninvasive is coming very soon
Thank You!

Robert.dibiasi@seattlechildrens.org