**Workshop: Aerosoltherapy**

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Aerosol Deposition and Particles Sizes

- Inertial impaction
  It occurs with larger (>3\(\mu\)m) fast-moving particles.

- Gravitational sedimentation
  It is a function of particle mass and time, with the rate of sedimentation proportional to particle size and mass.

- Diffusion
  It occurs with particles smaller than 1\(\mu\)m

AARC, A guide to aerosol delivery devices, 2013
Aerosol Deposition and Particles Sizes

- **Inertial impaction**: It occurs with larger (>3µm) fast-moving particles.

- **Gravitational sedimentation**: It is a function of particle mass and time, with the rate of sedimentation proportional to particle size and mass.

- **Diffusion**: It occurs with particles smaller than 1µm.

> *These mechanisms come into play as aerosol particles are inhaled orally or through the nose*
Aerosol Deposition and Particles Sizes

*Particle size* plays an important role in lung deposition, along with particle velocity and sedimentation time.

- Particle size of 1-5 µm are best for reaching the lung periphery
- Particle size of 5-10 µm deposit mostly in the conducting airways (large bronchi)
- Particle size of 10-100 µm deposit mostly in the nose
- Particle size of 1-5 µm are best for reaching the lung periphery

AARC, A guide to aerosol delivery devices, 2013
Effective administration

Patient-related factors:
- patient’s age
- physical and cognitive ability (ability to use a specific device, understanding of how and when to use)
- airways size, respiratory rate, breathing pattern, inspiratory flow

Device-related factors
- mouthpiece, face mask
- device (SVN,pMDI,DPI)

Drug-related factors
- availability
- combination

Environment and clinical factors
- when and where
- expertise
- education

AARC, A guide to aerosol delivery devices, 2013
**PICO**

*Patient/Population*
noninvasive ventilation OR positive ventilation OR mechanical ventilation OR positive pressure ventilation OR non invasive mechanical ventilation OR noninvasive ventilation OR "Noninvasive Ventilation"[Mesh] OR Positive-Pressure Respiration"[Mesh] OR "Intermittent Positive-Pressure Ventilation"[Mesh]

*Intervention*

*Database*
Medline (PubMed®) 1-15 March 2015

*Results 1562*

*Limits:* Systematic Reviews; Review; last 10 years, humans, adults

*Results 38 after limits*

+Hand search respiratory journals: 26 included
Effective (?) administration on Invasive and Non-invasive Ventilation

Ventilator-related
• Ventilation mode
• Tidal volume
• Respiratory rate
• Duty cycle
• Inspiratory waveform
• Breath-triggering mechanism

Device-related - MDI
• Type of spacer or adapter
• Position of spacer in circuit
• Timing of MDI actuation
• Type of MDI

Drug-related
• Dose
• Formulation
• Aerosol particle size
• Targeted site for delivery
• Duration of action

Patient-related
• Severity of airway obstruction
• Mechanism of airway obstruction
• Presence of dynamic hyperinflation
• Patient-ventilator synchrony

Circuit-related
• Endotracheal tube size
• Humidity of inhaled gas
• Density of inhaled gas

Type of Interface
Facemask
Nasal cannula

Device Related - nebulizer
• Type of nebulizer
• Fill volume
• Gas flow
• Cycling: inspiration vs continuous
• Duration of nebulization
• Position in the circuit

Device Related - pMDI
Type of spacer or adapter used
Timing of pMDI actuation
Position of pMDI/spacer

Drug Related
Dose
Aerosol particle size
Duration of action

Breathing Parameters
Mode of ventilation
Tidal volume
Respiratory rate
Inspiratory air flow
Pressure settings

Dhand, 2005/2012
Aerosol Deposition and Particles Sizes during Mechanical Ventilation

During MV, part of the aerosol is trapped in the ventilator circuit and the endotracheal tube.

Large droplet (>3 µm) are more likely to be trapped in the circuit, whereas smaller particles (<0.5 µm) diffuse and are more likely to be expelled during expiration.

To have a good alveolar deposition, the size of the particles generated should be, at best, 1-3 µm (lung periphery target)
Disease severity

The degree of lung disease at the time of inhalation significantly influences the pattern of drug deposition within the lungs.

Several studies have shown that central airway deposition is enhanced as mucus plugging, turbulent airflow and airway obstruction increase.

Laube, 2011
Disease severity

The degree of lung disease at the time of inhalation significantly influences the pattern of drug deposition within the lungs.

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→ Little or no drug may deposit in the lung periphery!

Laube, 2011
Nominal dose-lung dose

HFA pMDI (nominal dose)

actuator
ventilator circuit
ETT
exhaled
systemically absorbed
lung dose

HFA
27°C
RH < 30%

68.6%  9.4%  8.1%  1.3%
31.4%  23.3%

HFA
35°C
RH < 99%

57.2%  30.5%  18.1%  12.4%
42.8%  24.7%  12.3%

Humidifier

Dhand, 2005
The best lung dose

✧ **PRECISION**
Precision of lung dosing requires consideration of limiting drug losses, in order to target the drug to specific regions of the respiratory tract (larger airways versus more peripheral)

✧ **RELIABILITY**
Uniform amounts of drug should be deposited in the lung under a variety of conditions

✧ **CONSISTENCY**
Requires uniformity in drug-deposition across the life of the chosen device

Dhand, 2005
Delivery Device

- The choice is determined by the devices that are available for that drug (and those available at each hospital level).
- Correct cleaning, maintenance and disinfection procedures (that may change nebulizer performance in time)
Delivery Device

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Patients (and professionals) behaviour

- Adherence to treatment regimens is known to be frequently poor in all therapeutics areas
- Even if fully adherent, inhaled therapy may be ineffective if poor inhalation technique limits the amount of drug available for lung deposition
- Healthcare providers have a particular duty to ensure that patients or care-givers are able to use their inhalers effectively
The REVA survey
Réseau Européen de recherche en Ventilation Artificielle

- 15% response rate
- 611 departments in 70 countries

Aerosol therapy during mechanical ventilation: an international survey

- 99% reported using aerosol therapy during mechanical invasive/noninvasive ventilation
- 43% exclusively used nebulizers
- 55% also used metered dose inhalers
- Nebulization relied on jet (55%), ultrasonic (44%) and vibrating mesh nebulizers (14%)
- Bronchodilators and steroids were the most frequently delivered drugs

Conclusions

The use of aerosol therapy during MV appeared to be frequent for the delivery of bronchodilators and steroids and also to a lesser extent for the delivery of antibiotics. Scientific knowledge about optimal implementation of aerosol therapy during MV seemed to be applied infrequently and the use of some potentially dangerous practices was reported. These issues may be addressed through educational programs and research focusing on simplifying bench-to-bedside transfer of knowledge.
Intubated and mechanically ventilated patients

◆ pMDI and in-line spacer/holding chamber
  → Spacer/holding chamber tightly inserted into the respiratory limb side of the ventilator circuit, at ≈15 cm from the ETT.

◆ Nebulisers (jet/ultrasonic/mesh)
  → Jet nebulizers placed at a distance from the ETT. Addition of a reservoir between the nebulizer and ETT modestly increase efficiency of drug delivery.
  → Placement of ultrasonic proximal to or distal to Y-piece does not influence efficacy. The efficiency is doubled only with addition of a cylindric storage chamber (500/600 mL) in the inspiratory limb
  → Vibrating mesh have higher drug output and nominal dose, with negligible residual volume. These are still under investigation (but appears to be better suited for delivering inhaled drugs).

◆ In adults patients, a tidal volume of ≥500 ml guarantees drug delivery to the lower respiratory tract (if appropriate for the patient)

◆ No DPIs (may have promise for future use)

Laube, 2011, Ari 2010
pMDI

- **Priming and shaking the canister**
  Prime pMDI before first use and if it has not been actuated for more than 24h. Shake before the actuation of each dose

- **Placement of the pMDI**
  Placing the spacer chamber in the inspiratory limb 15 cm from ETT increases aerosol deposition with improved potential for clinical response.

- **Timing of actuation**
  Actuation of a pMDI must be synchronized with the precise onset of inspiration to maximize aerosol drug delivery; wait at least 15s between actuation

- **Heat and humidity**
  Removing the humidifier is not recommend for routine aerosol therapy. For inexpensive drugs (salbutamol or ipratropium bromide) increasing the administered dose of drug may be safer than turning off humidifier. For more expensive drugs, if a dry ventilator circuit is needed, a heat moisture exchanger should be employed and the medication administered within a short period (<10 minutes).

Ari 2012, Dhand 2008
Nebulizer efficiency

- **Type of nebulizer**
  Jet nebulizers are less efficient than ultrasonic and vibrating mesh (higher rate of nebulization in a shorter period of time). Mesh are associated with higher efficiency than jet or ultrasonic nebulizers.

- **Residual dead volume**
  Jet nebulizer have a higher residual volume, nebulize less of a proportion of the drug and do not function well with fill volumes < 2mL. Mesh have smaller residual volume than jet and ultrasonic nebulizers.

- **Position in the ventilator circuit**
  Placement of jet nebulizer farther from ETT improves aerosol delivery (the ventilator tubing acts as a spacer).

- **Bias flow**
  If increased, the amount of aerosol deposited decreased. During continuous nebulization, aerosol delivery could be enhanced by reducing bias flow to < 2 L/min.

- **Gas flow**
  Each model of jet nebulizers is designed to work best at specific flow (2-10 L/min). Ultrasonic and mesh are operated by electricity and they are not influenced by gas flow.

Ari 2012, Dhand 2008
Jet VS vibrating mesh nebulizers

Fink 2013
Optimal techniques for pMDI and Nebulizers

1. Review order, identify patient, and assess need for bronchodilator.
2. Assess airway, remove excess secretions.
3. Shake pMDI and warm to hand temperature (prime if not used within 24 h).
4. Place pMDI in adapter in ventilator circuit.
5. Remove HME. Do not disconnect humidifier.
7. Wait at least 15 s between actuations; administer total dose.
9. Reconnect HME.
Optimal techniques for pMDI and Nebulizers

1. Review order, identify patient, and assess need for bronchodilator.
2. Assess airway, remove excess secretions if present.
3. Place drug in nebulizer, do not exceed manufacturer recommendations
4. Place nebulizer in the inspiratory line 18 in (46 cm) from the patient wye connector or proximal to the ventilator.
5. Use minimal flow-by or continuous flow during nebulizer operation.
6. Remove HME from circuit (do not disconnect humidifier).
7. Set gas flow to nebulizer at 2–10 L/min, based on manufacturer label.
   a. Use ventilator to power nebulizer if it meets the nebulizer flow requirements and cycles on inspiration, or
   b. Use continuous flow from external source (~50 psi).
8. Adjust ventilator volume or pressure limit and alarms to compensate for added flow.
9. Run until nebulizer begins to sputter.
10. Remove nebulizer from circuit, rinse with sterile water and run dry, store in safe place.
11. Reconnect humidifier or HME, return ventilator settings and alarms to previous values.
13. Assess outcome and document findings.
MDIs VS Nebulizers (bronchodilator)

**P** mechanically ventilated adults with need for aerosol bronchodilator therapy in critical care units.

**I** pMDI

**C** nebulizers

**O**

1. Reduction in airway resistance, measured as a reduction in interrupter resistance ($R_{int}$) and additional effective resistance ($\Delta R_{ts}$)
2. Patient outcome, mortality during critical care unit admission
3. Patient outcome, duration of mechanical ventilation

1. Adverse changes to haemodynamic observations
2. Reduction in wheezing
3. Freedom from contamination
4. Quality of life
5. Practitioner satisfaction including ease of use and convenience

**Objective** Compare neb vs MDIs for bronchodilator delivery for invasively ventilated adults

**Type of study** RCTs

**Results** Three studies included with a total of 46 patients
MDIs VS Nebulizers
(bronchodilator)

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**Implications for practice**
Existing randomized controlled trials, including randomized cross-over trials where the order of the intervention was randomized, comparing a nebulizer and MDI for aerosol bronchodilation in mechanically ventilated adult patients do not provide sufficient evidence to support either delivery method at this time.

Holland 2013
MDIs VS Nebulizers
(bronchodilator)

- Fink et al. strongly advocate MDIs; this recommendation is based on drug deposition and aerosol delivery not on patient response assessed via respiratory variables. American Journal of Respiratory and Critical Care Medicine 1999;159:63–8.

- Hess et al. recommend the use of an MDI but, in agreement with Jantz et al., highlight the importance of optimal administration techniques to achieve the benefits associated with this delivery route. Chest 1991;100(4): 1103–4.

- Guerin et al. and Dhand et al. state that if an optimal administration technique is used, equal physiological end points may be achieved and either method of administration. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2008;21(1):85–96

- Bowton et al. demonstrated potential annual cost saving of 396,000$ when MDIs were substituted for nebulizer therapy. Chest 1992; 101(2):305–8.

- Dolovich et al and O’Doherty et al. concluded that no advantage exists with either method of administration and both MDI and nebulizer can be used to achieve successful bronchodilation. Chest 2005;127(1): 335–71.
Position of the patient

Most patients are recumbent or semi-recumbent while receiving mechanical ventilation and inhaled drug therapy.

Ventilator-dependent patients should preferably sit in bed or in a chair during inhalation therapy.

A semi-recumbent position (head of the bed elevated 20/30° above horizontal) should suffice.
Non-Invasive (NIV) ventilated patients

“Aerosol delivery in patients receiving noninvasive positive pressure ventilation is less efficient than that in patients receiving invasive mechanical ventilation.”

* Dolovich, Dhand

Lancet 2011; 377:1032-45
Options

✓ Remove the patient from NIV and administer inhaled drugs as patients can tolerate brief period of discontinuation (but patients may have still difficulty using the nebulizer or MDI optimally).

✓ Aerosol can be delivered by nebulizer placed in-line between the single limb circuit and the mask (on into the inspiratory limb if dual-limb circuit is present).

✓ A spacer chamber can be placed between the single limb circuit and the mask.
NIV and aerosol therapy

- High inspiratory flows increase turbulence and the associated high inertial forces cause greater particle impaction in central airways.

- Application of positive pressure reduces aerosol particle size, increase tidal volume, reduces respiratory rate: all of which enhance aerosol delivery.

- Increase in expiratory time (due to a slower respiratory rate) enhance particle sedimentation and alter the pattern of drug deposition during exhalation.

- PS or CPAP are helpful in reducing wob in patients with acute bronchoconstriction and this might influence the response to inhaled drugs.

Dhand 2012
Masks

A poorly fitting interface decreases clinical effectiveness and compliance of NIV therapy.

- For optimal aerosol delivery, facemask should produce a tight seal to avoid aerosol leakage and to reduce aerosol deposition around the eyes.

**Nasal Mask.** Aerosol deposition in nasal passages significantly reduces drug delivery to the lungs and could reduce bronchodilator efficacy compared to inhalation with a mouthpiece. 40 to 99% of the aerosol inhaled during NIV is likely to deposit in the nose. Mouth leaks.

**Oronasal Mask.** Considered as the first choice in patients with acute respiratory failure. Less tolerate in case of claustrophobia or frequent productive cough.
Evidences at a glance

- Nebulizer efficiency is higher with the leak port in the circuit compared to a leak port in the facemask.

- For bronchodilator therapy in patients with airflow obstruction, low levels of CPAP (5 cmH$_2$O) are just as effective for drug delivery as higher levels (≥10 cmH$_2$O).

- A moderate level of inspiratory pressure support (10-15 cmH$_2$O) seems to give the best results without the risk of delivering higher than normal tidal volumes.

- Intermittent operation of the nebulizer minimizes aerosol wastage during exhalation and is more efficient for aerosol delivery compared with continuous aerosol generation.

- Drug doses may need adjustment considering the known effects of humidity in reducing the efficiency of aerosol delivery.
Optimal techniques for pMDI and Nebulizers

- Assess patient, especially hemodynamic status, mask fit and tolerability, and patient-ventilator synchrony
- Minimize leaks in the mask and or circuit
- Place cylindrical spacer (volume ~140 mL) between circuit and mask
- Shake pMDI canister well and place it in the adapter of the spacer chamber
- Select modest level of CPAP (~5 cm H₂O) and inspiratory pressure support (10 to 15 cm H₂O)
- Humidify inspired air if patient is receiving NIPPV for >30 min
- Actuate pMDI at the beginning of inspiratory air flow from the ventilator
- Repeat actuations with at least 15 sec between actuations
- Monitor patient and assess clinical response
- Administer the specified number of doses
- Remove pMDI and chamber spacer and reconnect circuit
- Observe patient for any adverse effects

If a heat and moisture exchanger is employed, it should not be placed between the pMDI and the mouth because it will trap the drug particles.
Optimal techniques for pMDI and Nebulizers

- Assess patient, especially hemodynamic status, mask fit and tolerability, and patient-ventilator synchrony
- Minimize leaks in the mask and or circuit
- Fill nebulizer up to optimal fill volume (4 to 6 mL for a jet nebulizer)
- Place nebulizer upright between air leak in circuit and mask
- Select modest level of CPAP (~5 cm H₂O) and inspiratory pressure support (10 to 15 cm H₂O)
- Humidify inspired air if patient is receiving NIPPV for >30 min
- Operate nebulizer with gas flow of 6–8 L/min
- Tap nebulizer periodically until it sputters
- Monitor patient and assess clinical response
- Remove nebulizer form circuit, rinse with sterile water, air dry, and store in a clean space
- Reconnect circuit
- Observe patient for any adverse effects

Laube 2011/ Dhand 2012
Infection control

- It has been reported that nebulizer performance may change in time due to incorrect cleaning, maintenance, and disinfection procedures.

- It has been documented that aerosol generators used at home are frequently contaminated with bacteria.

- The importance of cleaning and maintaining aerosol equipment should be emphasized in IC education programs with patients and caregivers through repeated oral and written instructions.

AARC, A guide to aerosol delivery devices, 2013
Infection control

✓ Pressurized metered-dose inhalers
The plastic container of pMDI should be cleaned at least once a week.

✓ MDI accessory devices
When a spacer is used with a pMDI, it should be cleaned before first use and then periodically cleaned based on the manufacturer’s suggestions.

<table>
<thead>
<tr>
<th>Cleaning the pMDI</th>
<th>Cleaning the Chamber Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean once a week and as needed.</td>
<td>Clean every two weeks and as needed.</td>
</tr>
<tr>
<td>Look at the hole where the drug sprays out from the inhaler.</td>
<td>Disassemble the device for cleaning.</td>
</tr>
<tr>
<td>Clean the inhaler if you see powder in or around the hole.</td>
<td>Soak the spacer parts in warm water with liquid detergent and gently shake both pieces back and forth.</td>
</tr>
<tr>
<td>Remove the pMDI canister from the plastic container so it does not get wet.</td>
<td>Shake out to remove excess water.</td>
</tr>
<tr>
<td>Rinse the plastic container with warm water and shake out to remove excess water.</td>
<td>Air dry spacer parts in the vertical position overnight.</td>
</tr>
<tr>
<td>Dry overnight.</td>
<td>Do not towel dry the spacer as this will reduce dose delivery because of static charge.</td>
</tr>
<tr>
<td>Replace the canister back inside the mouthpiece and recap the mouthpiece.</td>
<td>Replace the back piece on the spacer when it is completely dry.</td>
</tr>
</tbody>
</table>

AARC, A guide to aerosol delivery devices, 2013
Infection control

✓ Nebulizers
Nebulizers should be cleaned after every treatment. The longer a dirty nebulizer sits and is allowed to dry, the harder it is to thoroughly clean. Rinsing and washing the nebulizer immediately after each treatment can go a long way in reducing infection risk.

Mesh and ultrasonic nebulizers should be cleaned and disinfected based on the manufacturer’s recommendations.

Equipment must be cleaned well with dish soap and water to remove all organic and inorganic debris before disinfection.

AARC, A guide to aerosol delivery devices, 2013
Infection control

Disinfection should occur once or twice a week. Equipment must be disinfected by either heat or cold disinfectant methods, as permissible by the manufacturer.

Heat methods
- immersion in continuously boiling water for 5 minutes;
- washing in a dishwasher if the equipment is dishwasher-safe and the water achieves a temperature greater than 70°C for 30 minutes;
- use of a microwave oven if the equipment is microwave safe and can be placed in a bowl of water in a home microwave oven (2.45 Ghz) for 5 minutes;
- use of electric steam sterilizer (eg, baby bottle sterilizer).

Cold methods
- soaking in 70%–90% ethyl or isopropyl alcohol for 5 minutes (avoid use near open flames) or in 3% hydrogen peroxide for 30 minutes.
- Vinegar (acetic acid) is not recommended because it has inadequate activity against some potential CF pathogens (eg, S. aureus).
- Bleach is no longer recommended because a 0.5% hypochlorite solution did not reduce the number of CF pathogens on home nebulizers.
Infection control

Final rinse, drying and maintenance
The patient should use sterile water for the final rinse. Sterile water can be prepared by boiling tap water and achieving a rolling boil for 5 minutes. Sterile water can become contaminated after use and/or storage, but the frequency of this is unknown. Boiling water immediately before use minimizes this possibility. Distilled water is not recommended for cleaning or rinsing respiratory therapy equipment since contamination with *B. cepacia* complex can occur during the manufacturing process.

Because bacteria grow in wet, moist places, nebulizers should be thoroughly dried and stored in a clean dry place between treatments.

Saiman 2014/AARC, A guide to aerosol delivery devices, 2013
Infection control – hospital

The CF Foundation recommends the following:

a. Nebulizers are for single-patient use only
b. Aseptic technique is always followed when handling the nebulizer and dispensing medications
c. Single-dose vials of medication used in nebulizers are always preferred
d. Handheld disposable nebulizers are managed as follows:
   - i. After each use, rinse out residual volume with sterile water and wipe mask mouthpiece with an alcohol pad
   - ii. Discard the nebulizer every 24 hours
e. Handheld reusable nebulizers (e.g., home equipment) are managed as follows:
   - i. After each use, clean, disinfect, rinse with sterile water (if applicable, following cold disinfection method), and air dry away from sink
   - ii. After each use, the nebulizer can be reprocessed (e.g., by steam sterilization) if the reprocessing is performed according to the manufacturer’s instructions and the CF

Saiman 2014
Dr. House - “Anna, are you using your inhaler?”
Anna – “All the time”