Inhaled Medications
Considering all the Options, How do you Choose?

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Disclaimer

• No conflict of interest
• No financial disclaimers
Objectives

• Establish what constitutes an aerosol and provide a brief physiological review of the medication that we administer
• Examine delivery options and demonstrate how to optimize each one
• Discuss how we can choose the best device for any given patient
Background of Aerosol Therapy

- Medical aerosol
  - Any suspension of liquid or solid drug in a carrier gas
- Aerosol drug therapy
  - Generating aerosols
  - Formulating drugs
  - Administering medications
Background of Aerosol Therapy

Inhaled aerosol medications for the treatment of pulmonary diseases became well-established in the last half of the 20th century.
Background of Aerosol Therapy

Ceramic Inhalers
19th Century

Atomizers
Steam Inhalers
Asthma Cigarettes and powders
Mid-Late 19th Century

Hand bulb nebulizer
Early nebulizers using electricity and compressed air
1930s-1940s

Nebulizers
Jet and Ultrasonic

Nebulizers with special features

Metered Dose Inhalers

pMDI
1950s

Spacers and DPIs
1970s

Phase out CFC
1980s

Soft Mist
2011
Physiology

• How does our inhaled aerosol reach its target in the lung?
  • Nervous system involvement
    • Bronchodilators
      • Short acting beta2 adrenergic (SABA)
      • Long acting beta2 adrenergic (LABA)
    • Short acting muscarinic antagonist (SAMA) or
      • Short acting anticholinergic (SAAC)
    • Long acting muscarinic antagonist (LAMA) or
      • Long acting anticholinergic (LAAC)
  • Corticosteroids
  • Mucolytics
  • Antibiotics
Physiology of Medications: Bronchodilation

Parasympathetic
- Constricts pupil
- Stimulates salivation
- Inhibits heart
- Constricts bronchi
- Stimulates digestive activity
- Stimulates gallbladder
- Contracts bladder
- Relaxes rectum

Sympathetic ganglia

Sympathetic
- Dilates pupil
- Inhibits salivation
- Relaxes bronchi
- Accelerates heart
- Inhibits digestive activity
- Stimulates glucose release by liver
- Secretion of epinephrine and norepinephrine from kidney
- Relaxes bladder
- Contracts rectum

Anticholinergics
- Antimuscarinics

Sympathomimetics
- Beta 2 Agonists
Bronchodilation

- **SYMPATHETIC NERVOUS SYSTEM**
- Relief of: wheezing, shortness of breath, cough
- Sympathomimetics or Beta 2 Agonists
  - SABA
    - Albuterol Sulfate
    - Levalbuterol
- Long Acting Bronchodilators
  - LABA
    - Formoterol
    - Salmeterol
Bronchodilation

- **PARASYMPATHETIC NERVOUS SYSTEM**
  - Relief of: cough, sputum production, shortness of breath
  - Anticholinergic or muscarinic antagonist
    - SAAC or SAMA
      - Ipratropium
    - LAAC or LAMA
      - Tiotropium
Combination

- SAMA and SABA
  - Ipratropium Bromide and Albuterol
- Different mechanisms
- Maximizes bronchodilation effect
Corticosteroids

**Inflammatory cells**
- Eosinophil
  - ↓ Numbers (apoptosis)
- T-lymphocyte
- Cytokines
  - ↓ Numbers
- Mast cell
- Macrophage
- Dendritic cell

**Structural cells**
- Epithelial cell
  - ↓ Cytokines
- Mediators
- Endothelial cell
  - ↓ Leak
- Airway smooth muscle
  - ↑ β2-Receptors
  - ↓ Cytokines
- Mucus gland
  - ↓ Mucus secretion
Corticosteroids

- ANTI-INFLAMMATORY
  - Mometasone
  - Fluticasone
  - Budesonide
- Maintenance medications
- Inhaled vs oral/IV
- Spacer and mouth rinsing
Combination

- LABA & Corticosteroid
  - Fluticasone & Salmeterol
  - Fluticasone & Vilanterol
  - Mometasone & Formoterol
  - Budesonide & Formoterol
Mucolytics

- Alter consistency of gel layer of mucus
  - N-acetylcysteine
  - Sodium bicarbonate
  - Dornase alpha
Antibiotics

• Treatment of chronic pulmonary infections
  • Tobramycin
  • Aztreonam (Cayston)
  • Pentamidine

• Nebulizer selection
  • FDA approval
  • Particle size
Delivery Options
What’s Important?

- Particle size or Mass Median Aerodynamic Diameter (MMAD)
  - Mass equally divided
- Respirable fraction
- Inhaled respiratory mass per breath
- Inhaled respiratory output rate
- Inhaled drug mass
## Particle Size

**MMAD:** Mass median aerodynamic diameter

<table>
<thead>
<tr>
<th>Location</th>
<th>MMAD particle size, µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nose or mouth to larynx</td>
<td>10 or larger</td>
</tr>
<tr>
<td>Trachea to terminal bronchioles</td>
<td>9-5</td>
</tr>
<tr>
<td>Respiratory bronchioles</td>
<td>5-2</td>
</tr>
<tr>
<td>Lung parenchyma (alveoli)</td>
<td>1-3</td>
</tr>
</tbody>
</table>

*Stridor*
Particle Size

The effect of aerosol particle size on the site of preferential deposition in the airways
Delivery Options

- Small Volume Nebulizer
  - Jet:
    - Uses compressed gas to aerosolize a liquid medication
    - Least expensive nebulizer
    - Factors affecting performance
    - Different types
Delivery Options

- Small Volume Nebulizer
  - Jet:
    - Pneumatic with reservoir tubing
    - With collection bag
    - Breath enhanced
    - Breath actuated
Delivery Options

- Small Volume Nebulizer
  - Ultrasonic:
    - Convert electrical energy to high-frequency vibrations using a transducer
    - Use with bronchodilators and saline, but not budesonide

![Diagram of the Ultrasonic Nebulizer](image)
Delivery Options

• Vibrating Mesh:
  • Uses electricity and piezo element
  • Slow moving aerosol
  • Very efficient and results in minimal residual volume
  • Active vs Passive
Delivery Options

• Specific application:
  • Ribavirin administration with a small particle aerosol generator (SPAG)
  • Pentamidine administration via a SVN with a inspiratory/expiratory one-way valve
Optimal Technique SVN

- Breathing pattern
- Treatment ends at the “SPUTTER”
- Mouthpiece vs Mask
Inhalers
Delivery Options
Delivery Options

- pMDI:
  - Most common aerosol generator prescribed for patients with COPD and asthma
  - Conventional
  - Factors affecting performance
  - Spacer/valve holding chamber
  - Technique
Delivery Options

- DPI:
  - Inspiratory flow driven
  - Single dose, multiple dose
  - Factors affecting performance
  - Technique
Delivery Options

- Respimat: soft mist
  - Portable
  - Advantages
  - Disadvantages
  - Technique
What else...
Special Considerations in the Hospital Setting...

- Effectiveness of aerosol delivery in patients requiring mechanical ventilation
  - Device
  - Position
  - Ventilator and circuit
  - Presence of bias flow
  - Patient age and synchrony
Evaluation of Aerosol Generator Devices at 3 Locations in Humidified and Non-humidified Circuits During Adult Mechanical Ventilation

- **Device**
  - Jet
  - Vibrating Mesh
  - Ultrasonic
  - pMDI with spacer

- **Positions**
  - Between ETT and Y
  - 15 cm from Y
  - 15 cm from ventilator

- **No Bias Flow!**
Ari et al.

• Results:

• Inconclusive in terms of which is best
  • 2.5%-30% of drug delivered to filter

• ALL devices had about twice the delivery with the non-humidified circuit than with the humidified
  • But the benefits outweigh the risk!

• The jet neb provided the most efficient treatment when placed proximal to the ventilator

• MDI, mesh and USN provided the most efficient treatment when placed 15 cm from Y piece

• NO BIAS FLOW!
Ari et al.

**Influence of Nebulizer Type, Position, and Bias Flow on Aerosol Drug Delivery in Simulated Pediatric and Adult Lung Models During Mechanical Ventilation**

- **Device**
  - Misty Finity (jet neb)
  - Aerogen solo (vibrating mesh)
- **Position 1**
  - Jet neb: 15 cm from Y adapter
  - VM: between Y and circuit (manufacturer)
- **Position 2**
  - Jet neb: proximal to vent, prior to heater
  - VM: t-piece adapter at heater inlet
Fig. 1. Lung model of aerosol delivery with jet nebulizer (A) and vibrating-mesh nebulizer (B). The model includes a dual-chamber test lung, aerosol-collection filter, endotracheal tube, ventilator circuit, heated humidifier, and mechanical ventilator. The nebulizer circuit positions are shown.
Ari et al.

Fig. 2. Effect of position and bias flow on inhaled dose percent with a vibrating-mesh nebulizer and a jet nebulizer with adult and pediatric lung models. * Difference statistically significant.
Ari et al.

• Results:
  • Less drug delivered with higher bias flows

  • Vibrating mesh provided the most drug delivery

  • Vibrating Mesh:
    • Adult and Pediatric: heater inlet

  • Jet Nebulizer:
    • Adult and Pediatric: proximal to vent; prior to heater
There’s more...
Noninvasive

- Systematic Review
  - Nebulizers (jet and vibrating mesh) vs MDI
- Circuit leaks: interface vs circuit
- Positioning

Greater aerosol delivery with higher pressure support and low expiratory pressure

Effect of humidification on aerosol delivery during NIV has not been studied

Aerosol generator between leak port and mask

Breath-actuation has not been studied with NIV
Noninvasive

• Results
  • Both MDIs and nebs can be therapeutic

• Positioning depends on leak
  • MDI: spacer placed between circuit and mask
  • Jet: placed after leak in circuit
  • Vibrating mesh: in interface if possible or between exhalation port and interface

• Less medication delivered if SVN placed prior to heater
High Flow Nasal Cannula

- Systematic Review 2015
- Aerosol delivery with a standard HFNC at high flows is likely to be low due to:
  - High flows (greater than 10L/min) = turbulence
  - Sharp changes in aerosol flow, humidification, nasal prongs
- Results
  - No great options
  - Clinical judgment
  - New study:
    - Respirable mass: 2-10%
    - Therapeutic effects
    - Breathing patterns
Just one more thing!
What about the kids...

- MDI vs Nebulizer

AARC Pediatric Guidelines for Aerosol Delivery Devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVN with mask</td>
<td>≤ 3 years</td>
</tr>
<tr>
<td>SVN with mouthpiece</td>
<td>≥ 3 years</td>
</tr>
<tr>
<td>pMDI with holding chamber/spacer and mask</td>
<td>&lt; 4 years</td>
</tr>
<tr>
<td>pMDI with holding chamber/spacer</td>
<td>≥ 4 years</td>
</tr>
<tr>
<td>DPI</td>
<td>≥ 4 years</td>
</tr>
<tr>
<td>MDI</td>
<td>≥ 5 years</td>
</tr>
<tr>
<td>Breath-actuated MDI</td>
<td>≥ 5 years</td>
</tr>
<tr>
<td>Breath-actuated nebulizer</td>
<td>≥ 5 years</td>
</tr>
</tbody>
</table>

“blow by” is not an effective treatment
What about the kids...

- Systematic Review
- Noninvasive Ventilation
  - HFNC: jet neb setup vs vibrating mesh inline
  - NCPAP: vibrating mesh at two positions
- Mechanical Ventilation
  - Jet neb vs vibrating mesh; positioning
  - Infant vs pediatric
- HFOV
  - Positioning
  - Pediatric
What about the kids...

• Results
  • HFNC
    • More drug delivered with vibrating mesh with facemask than inline
  • Bubble CPAP
    • Vibrating mesh placed at the humidifier
  • Mechanical Ventilation
    • Infant: vibrating mesh proximal to Y in circuit (w/bias flow)
    • Pediatric: vibrating mesh at the humidifier
  • HFOV
    • Vibrating mesh between ETT and Y in circuit
Are we done yet?
What to take away...

- Selection is very important for optimizing the results of aerosol drug therapy.

- Evidence indicates all delivery devices can be equally effective if used correctly.

- Criteria to select a device can be divided into four categories:
  - Patient-related
  - Drug-related
  - Device-related
  - Environmental and clinical factors
RESPIRATORY THERAPY

...because, if they aren't breathing, they aren't doing anything else, either.
References


