Emergent Management of Pediatric Asthma: Myths & Pitfalls

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Disclosures and Conflicts of Interest

- I have no conflicts of interest in relation to this presentation
Learning Objectives

• Summarize the prevalence and financial impact of asthma in the pediatric population
• Prioritize a systematic approach for acute management
• Identify advanced treatment modalities
• Evaluate common pitfalls in management

Epidemiology

• 8.4% prevalence in US children
  – Rate of emergency care use 2-2.5 times higher in age <18 yrs
• Minorities disproportionately affected*
  – Mortality 4-5 times higher in black compared to white children
  – Puerto Ricans have highest prevalence
  – Role of allergen exposure
  – Reliance on episodic/emergent care
  – Decreased medication compliance

Epidemiology

Cost of Asthma

- Annual health care cost for child with asthma: $1042
  - Child without asthma: $618
- Children with asthma miss 2.48 school days/year

Pathophysiology

Trigger Factor

Airway Inflammation

- Reduce Inflammation
- Reverse Obstruction
- Correction of Hypoxemia

Narrow Breathing Passages

Wheezing, Cough, Shortness of Breath, Tightness in Chest
Bronchodilators

- Inhaled SABA (Albuterol)
- Ipratropium bromide
- Parental beta-agonists
- Magnesium sulfate
- Ketamine

Continuous vs. Intermittent

- Cochrane Database Systematic Review, 2003
  - RCTs of continuous vs. intermittent inhaled beta-agonists in ED
  - 8 trials
  - Continuous treatments associated with greater improvement in spirometry and reduced rates of hospital admissions

Inhaled SABA

- **Goal** = Administer 3 doses within the first hour
- **Continuous vs. Intermittent**
  - Similar outcomes and side effects
  - Continuous less labor intensive
  - Intermittent may be better tolerated by younger children

**Recommendation**
Continuous therapy for moderate to severe asthma exacerbation

Nebulizer vs. MDI
Nebulizer vs. MDI

- **Nebulizer**
  - ✖ Required to hold treatment over patient’s face (≈60 minutes)
  - ✖ Machine sanitation
  - ✖ Machine are not portable
  - ✔ Passive administration
  - ✔ Supplemental humidified oxygen
  - ✔ Co-administration of other inhaled meds (ipratropium)

- **Meter-dosed Inhaler**
  - ✖ Requires patient coordination and education
  - ✖ Requires respiratory hold
  - ✖ Requires spacer & mask
  - ✔ Portability
  - ✔ Treatment Time
  - ✔ No external power source
  - ✔ Cost in the community


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**Nebulizer vs. MDI**

- *Cochrane Database Systematic Review, 2014*
  - 39 Trials, 1897 children

**Hospitalization Admission Rates**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chong-Neb 2005</td>
<td>11.4%</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Chou 1995</td>
<td>4.6%</td>
<td>0.91 [0.25, 3.27]</td>
<td>0.57 [0.05, 6.11]</td>
</tr>
<tr>
<td>Direkwanachai 2008</td>
<td>19.1%</td>
<td>0.45 [0.14, 1.47]</td>
<td>0.56 [0.31, 1.00]</td>
</tr>
<tr>
<td>Jamali 2006</td>
<td>7.2%</td>
<td>1.03 [0.23, 4.73]</td>
<td>2.05 [0.55, 7.63]</td>
</tr>
<tr>
<td>Leversha 2000</td>
<td>6.8%</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Ploin 2000</td>
<td>100.0%</td>
<td>0.71 [0.47, 1.08]</td>
<td>0.71 [0.47, 1.08]</td>
</tr>
</tbody>
</table>

*Chamber better* vs. *Nebuliser better*

Nebulizer vs. MDI

**ED Length of Stay**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Mean Difference (IV, Random, 95% CI [mins])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.32 Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chou 1995</td>
<td>26.2%</td>
<td>-37.00 [-50.43, -23.57]</td>
</tr>
<tr>
<td>Durante 2002</td>
<td>40.3%</td>
<td>-25.80 [-32.82, -18.88]</td>
</tr>
<tr>
<td>Sannier 2007</td>
<td>33.5%</td>
<td>-40.00 [-50.00, -30.00]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>-33.48 [-43.32, -23.65]</td>
</tr>
</tbody>
</table>

**Heart Rate**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Mean Difference (IV, Random, 95% CI [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9.2 Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batra 1997</td>
<td>13.0%</td>
<td>-5.40 [-10.74, -0.06]</td>
</tr>
<tr>
<td>Chong-Neto 2005</td>
<td>7.4%</td>
<td>-12.30 [-21.13, -3.47]</td>
</tr>
<tr>
<td>Chou 1995</td>
<td>14.2%</td>
<td>-10.00 [-14.74, -5.26]</td>
</tr>
<tr>
<td>Durante 2002</td>
<td>7.2%</td>
<td>-5.00 [-14.03, 4.03]</td>
</tr>
<tr>
<td>Jamali 2006</td>
<td>13.3%</td>
<td>-1.00 [-6.16, 4.16]</td>
</tr>
<tr>
<td>Leversha 2000</td>
<td>16.8%</td>
<td>-7.15 [-10.79, -3.51]</td>
</tr>
<tr>
<td>Sannier 2007</td>
<td>7.8%</td>
<td>-2.60 [-8.07, 11.27]</td>
</tr>
<tr>
<td>Vazquez 1992</td>
<td>0.0%</td>
<td>-10.00 [-18.37, -1.63]</td>
</tr>
<tr>
<td>Yasmin 2012</td>
<td>12.4%</td>
<td>-0.60 [-6.20, 5.00]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>100.0%</td>
<td>-5.41 [-8.34, -2.48]</td>
</tr>
</tbody>
</table>

**Recommendation**

Nebulizers are equally as effective as MDI

**A Word About Spacers**

- Corrects for poor coordination/technique
- Decreases oropharyngeal deposition
- Improved outcomes in children with asthma

**Recommendation**
All Children Need a Spacer & Mask

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**Levalbuterol**

- Xopenex - Pure R-albuterol
- S-albuterol thought to be a weaker bronchoconstrictor
- Is it more effective?

*Xopenex HFA*®
(levosalbuterol tartrate) Inhalation Aerosol
Levalbuterol

- *Journal of Asthma, 2011*
  - 99 children, ED visits for mod/severe exacerbation
  - 7.5 mg albuterol vs. 3.75 mg levalbuterol
    - Further treatments given with same meds
    - Standard care; Double-blinded
  - After one hour, spirometry and asthma scores showed greater improvement in albuterol group
    - No differences in side effects, HR, RR, SaO₂
    - No difference in admission rate


Levalbuterol

- *Pulmonary Pharm Therapeutics, 2013*
  - Large meta-analysis and systemic review
  - 7 trials, 1625 patients
  - Similar RR, SaO₂, %ΔFEV₁, Clinical Asthma Scores
  - Levalbuterol should not be used over albuterol

Decreased Tachycardia?

- *Journal of Ped Pharm Therapy*, 2011
  - Levalbuterol vs. Racemic Albuterol x 3 doses
  - 50 patients
  - **No clinically significant difference in HR changes**

- *Annals of Pharmacotherapy*, 2013
  - Children with CHD, cardiomyopathy, or SVT
  - 192 patients
  - **Equivalent increases in HR**


Levalbuterol

- Does it cost more?
  - YES! 4-5 x more expensive for equivalent neb nose

**Recommendation**

Racemic albuterol with rare exception
Ipratropium Bromide

• Anticholinergic agent
• Impairs bronchial smooth muscle contraction
• Minimal systemic side effects
  – Unable to cross from lung to systemic circulation

Ipratropium Bromide

• Additive effect with SABA*
  – Improved spirometry measures
  – Reduced risk of hospitalization
• No benefit to continuing as inpatient**

Recommendation
Combine ipratropium bromide (2-3 doses) with first 3 doses of albuterol given over 1st hr

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Parental Beta-Agonists

- Subcutaneous or Intramuscular
- Poor inspiratory air flow or cooperation (i.e. AMS)
- Given within minutes of arrival
- Dosing
  - Terbutaline: 0.01 mg/kg/dose (Max dose 0.4 mg)
  - Epinephrine: 0.01 mg/kg/dose (Max dose 0.4 mg)
  - Consider auto injectable epinephrine

Parenteral Beta-Agonists

- Pediatric Emergency Care, 2007
  - Prospective RCT of IV Terbutaline
  - 49 children in ICU
  - Trend toward improved scores and shorter ICU stay, but not statistically significant

- Cochrane Review, 2012
  - 3 studies, 157 children
  - Limited evidence to support use of IV beta agonists


### Parental Beta-Agonists

- Increased side effects
  - Dysrhythmias, myocardial ischemia, hypertension
- Reserved for critically ill, poorly responsive
- Consider repeated doses (x3) vs. infusion
- Discuss with ICU colleagues

### Systemic Glucocorticoids

- Reduce airway edema and secretions
- Indicated in most children presenting to ED
  - Any moderate or severe exacerbation
  - Any mild exacerbation not responding to adequate home therapy
Systemic Glucocorticoids

Forrest Plot: Any steroid vs. placebo, outcome hospital admission

### Hospitalization Rates

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Total CS Events</th>
<th>Total Placebo Events</th>
<th>Total Weight</th>
<th>Odds Ratio (M-H, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connell 1994a</td>
<td>13</td>
<td>15</td>
<td>18</td>
<td>0.43 [0.09, 2.09]</td>
</tr>
<tr>
<td>Connell 1994b</td>
<td>7</td>
<td>12</td>
<td>16</td>
<td>0.16 [0.03, 0.77]</td>
</tr>
<tr>
<td>Lin 1997</td>
<td>7</td>
<td>23</td>
<td>5</td>
<td>1.49 [0.39, 5.65]</td>
</tr>
<tr>
<td>Lin 1999</td>
<td>8</td>
<td>30</td>
<td>11</td>
<td>0.50 [0.16, 1.52]</td>
</tr>
<tr>
<td>Littenberg 1986</td>
<td>9</td>
<td>49</td>
<td>23</td>
<td>0.26 [0.10, 0.65]</td>
</tr>
<tr>
<td>Rodrigo 1994</td>
<td>4</td>
<td>49</td>
<td>5</td>
<td>0.78 [0.20, 3.11]</td>
</tr>
<tr>
<td>Scarfone 1993</td>
<td>11</td>
<td>36</td>
<td>19</td>
<td>0.46 [0.16, 1.19]</td>
</tr>
<tr>
<td>Schneider 1998</td>
<td>5</td>
<td>27</td>
<td>12</td>
<td>0.28 [0.08, 0.97]</td>
</tr>
<tr>
<td>Stein 1990</td>
<td>21</td>
<td>44</td>
<td>23</td>
<td>0.95 [0.42, 2.17]</td>
</tr>
<tr>
<td>Storr 1987</td>
<td>53</td>
<td>73</td>
<td>65</td>
<td>0.08 [0.02, 0.36]</td>
</tr>
<tr>
<td>Tall 1990</td>
<td>4</td>
<td>17</td>
<td>4</td>
<td>0.69 [0.14, 3.52]</td>
</tr>
<tr>
<td>Wolfson 1994</td>
<td>17</td>
<td>42</td>
<td>15</td>
<td>1.41 [0.59, 3.36]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>426</strong></td>
<td><strong>418</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.50 [0.31, 0.81]</strong></td>
</tr>
</tbody>
</table>

Total events: 159

Heterogeneity: Tau² = 0.32; Chi² = 21.27, df = 11 (P = 0.003); I² = 48%
Test for overall effect: Z = 2.68 (P = 0.004)


### Systemic Glucocorticoids

- The sooner the better!
- Early administration (within 1 hr) vs. placebo*
  - Reduced admission rates
  - NNT to prevent one admission = 8

\[
NNT = \frac{1}{[(159/426) - (209/418)]} = 7.88 \approx 8
\]

Systemic Glucocorticoids

- Prednisone vs. Dexamethasone vs. Methylprednisolone
  (2mg/kg)             (0.6 mg/kg)                    (2 mg/kg)
- Effects start in 1-3 hours, max effect at 4-8 hours
- Inhaled glucocorticoids?
  - Thus far, no benefit in acute management

**Recommendation**
Systemic steroids recommended to non-responders to inhaled beta-agonists


Dexamethasone vs. Prednisone

- Pharmacokinetics
  - 5-6 times more potent than prednisone
  - 4-5 times longer half life
- Clinical
  - Similar efficacy with less side effects (i.e. vomiting)*
  - Single Dose or Two-Doses not inferior to prednisone**
  - No increase in unscheduled medical evaluations

Dexamethasone vs Prednisone

• Increased Compliance
  – Families prefer shorter duration*
  – More palatable and preferred by pediatric patients**

• Economic Cost Savings***
  – Less return visits
  – Less admissions


Kitchen Sink

• Beta Agonists (naturally)
• Inhaled anticholinergics (useful in first hour)
• IV steroids (struggling to breath ≠ PO)
• Magnesium sulfate
• Heliox
• Ketamine
Magnesium Sulfate

- Mechanism multifactorial
  - Smooth muscle relaxation
    - Blocks NMDA receptor-gated Ca channel
  - Reduces inflammatory mediators
    - Stabilizes T cells, inhibits mast cell degranulation
  - Stimulates nitric oxide synthesis
  - Rapid onset
Magnesium Sulfate

- When added to SABA and steroids:
  - Improved pulmonary function
  - Reduced inpatient hospitalization
  - No effect on SBP/DBP
- Dose: 25-75 mg/kg (max 2g) over 20 minutes

**Recommendation**
Consider magnesium in severe exacerbations who deteriorate despite initial therapy


Ketamine

- Bronchodilator effect
  - Central catecholamine release
  - Inhibition of vagal pathways → anticholinergic effect on bronchial smooth muscle
- Medication of choice for sedation/analgesia required for endotracheal intubation in asthmatics
Ketamine

- Utility in non-intubated children?
- Annals of Emergency medicine, 2005
  - Double-blind, randomized, placebo-controlled trial
  - 68 patients with continued mod-sever symptoms after initial conventional therapy
  - No benefit

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Heliox

- Increases efficient laminar flow
- 70:30 or 80:20 mixture

Re = \frac{\rho v r}{\eta}

*Re = Reynolds Number
\rho = density
v = velocity
R = radius
\eta = viscosity

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Heliox

• Benefits
  – Better lung mechanics
  – Improves albuterol delivery
  – Few side effects/complications (inert gas)

• Drawback
  – Expensive
  – Contraindicated in hypoxia
  – Few proven RCTs
  – Does not treat causative issue


Common Pitfalls

• Intubation Risk
• Excessive IVF
• Elevated lactic acidosis
• Transient hypoxia with β-agonist
Endotracheal Intubation

• Goal = DON’T INTUBATE
  – ¼ of children intubation develop complications
    • Pneumothorax
    • Impaired Preload
    • Cardiovascular Collapse
  – Mechanical ventilation associated with increased mortality

Endotracheal Intubation

• Indications
  – Apnea/Coma
  – Worsening mental status
  – Exhaustion
  – Refractory hypoxemia
  – Significant refractory respiratory acidosis (worsening despite maximal therapy)
**IV Hydration**

**Dehydration**
- Thickened secretions & mucous plugging
- Decreased preload
- \( CO = HR \times Preload \)

**Over-hydration**
- Negative intrapleural pressure
- Increased afterload
- Pulmonary Edema

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**Hydration Study**

- Am J Resp & Crit Care Medicine, 2018
  - Retrospective cohort, Urban Children’s Hospital
  - 1175 admitted asthmatic patients
  - **Positive fluid balance is associated with longer LOS, treatment duration, and oxygen utilization**
  - Prospective Validation Cohort (123 patients)
    - Correlated with fluid balance (B-lines)
    - Correlated with intrapleural pressure (Δ Peak Aortic Velocity)
  - **1% fluid overload = 7 hours hospital LOS**

V/Q Mismatch

- β-agonist worsens V/Q mismatch
- Transient hypoxia (≈10 min)

**Lactic Acidosis**

- β-agonist → derangement of glucose metabolism
- Increase Type B lactic acidosis
- Metabolic acidosis → compensatory hyperventilation
- Common with severe asthmatics and continuous albuterol

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**Beyond the First Hour**

- **Marked Improvement**
  - Observe at least one hour and reassess

- **Partial Improvement**
  - Continued observation (more time for steroids to take action?)
  - Consider further albuterol therapy (continuous vs frequent intermittent)
  - Reassess for appropriate disposition

- **No Improvement**
  - Consider other diagnoses
  - Hospitalization (Inpatient vs. ICU)
  - Escalate care (IV Mag sulfate, IV terbutaline, etc) vs. continuous inhaled therapy with albuterol
Take Home Points

- Get steroids onboard early
  - Decadron = Prednisone
- Duoneb x 3 in first hour
- MDI - Spacer = Nebulizer
- Advance therapies (continuous, magnesium, parental beta-agonist)
- Avoid pitfalls (V/Q mismatch, lactic acidosis, IVF)

References

References


Questions/Evaluation

https://survey.az1.qualtrics.com/jfe/form/SV_0cuBSHq4y5LGc3X