Ketamine in Severe Acute Asthma Exacerbations: What’s so “special” about ketamine?

Amanda L. Fowler, PharmD
PGY1 Pharmacy Practice Resident
University Health System, San Antonio, Texas
Division of Pharmacotherapy, The University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center,
University of Texas Health Science Center at San Antonio

January 17, 2014

Learning Objectives:
1. Describe the epidemiology, pathophysiology and standard management of severe asthma exacerbations
2. Identify patient with asthma exacerbation refractory to standard therapy
3. Evaluate bronchodilator properties of ketamine
4. Indicate ketamine’s role in the management of severe refractory asthma exacerbations
Asthma

1. Background\(^{1,2,3}\)
   a. Epidemiology
      i. Increased prevalence in the United States (US) from 2001 to 2009
         1. Adults: 7.3% to 8.2%
         2. Children: 8.7% to 9.6%
      ii. Most prevalent chronic disease in children
           1. Higher in low-income (13.5%) and non-Hispanic African American children (17.0%)
      iii. 1 in 12 people in the US have asthma
           1. ~25 million people
      iv. Asthma accounts for 2 million emergency department (ED) visits annually
           1. 6% to 13% require hospitalization
           2. 1 in 2 people with asthma had an attack in 2008
              a. ~12 million people
      v. Death due to asthma is uncommon
         1. 4,000 deaths annually in the US
         2. Death rate was 0.15 per 1,000 persons with asthma in 2007 – 2009
   b. Cost of Asthma
      i. $56 billion in total cost to the US in 2007
         1. Includes Direct medical expenses, lost school and work days, and early death

Figure 1. Current asthma prevalence among adults, 2009\(^{3}\)
2. Pathophysiology\textsuperscript{5,6,7} 
   a. Combination of genetic factors and environmental risk factors present  
   i. Genetics account for 60-80\% of the disposition to develop asthma  
      1. Polygenic  
      2. Genetic predisposition for atopy is a risk factor, not a strict determinant  
   ii. Environmental risk factors vary widely, including but not limited to:  
      1. Urbanization  
      2. Socioeconomic status  
      3. Allergen exposure  
      4. Decreased exposure to common childhood infectious agents  
   b. Major characteristics of asthma  
   i. Airway inflammation (Figure 2)  
      1. Inflammatory cell mediated  
      2. Allergens bind membrane-bound immunoglobulin E (IgE) on inflammatory cells  
      3. Release of pro-inflammatory mediators and cytokines  
         a. Smooth muscle contraction, mucus secretion, vasodilation  
         b. Recruitment of additional inflammatory cells  
      4. Vasodilation allows for plasma exudation from the pulmonary microvasculature  
         a. Airway wall becomes thick and edematous $\rightarrow$ airway narrowing/airflow obstruction  
         b. Mucus clearance reduced which may lead to mucus plug $\rightarrow$ airflow obstruction  

Figure 2. Airway inflammation in asthma\textsuperscript{5}  

ii. Airway hyperresponsiveness  
   1. Exaggerated bronchoconstrictor response to a variety of stimuli  
   2. Inflammation a major factor in determining degree of hyperresponsiveness  
iii. Airflow obstruction  
   1. Bronchoconstriction, airway edema, mucus hypersecretion, and/or airway remodeling  
   2. Airway smooth muscle  
      a. Surrounds airway lumen in a cylindrical fashion  
         i. Contraction creates sphincter-like motion  
      b. Bronchial smooth muscle neural innervations  
         i. Parasympathetic innervation  
            1. Maintains normal airway smooth muscle tone  
            2. Effect in small bronchi > bronchioles  

Acute Asthma Exacerbations  

1. Definition\textsuperscript{7}  
   a. All three major characteristics of asthma come together to acutely cause any one or combination of the following:  
      i. Shortness of breath  
      ii. Cough  
      iii. Wheeze  
      iv. Chest tightness  
      v. Decrease in respiratory flow  
         1. Measured by spirometry or peak expiratory flow (PEF) meters  
            a. Gold standard: forced expiratory volume in one second (FEV\textsubscript{1})  
            b. PEF correlates with FEV\textsubscript{1}  

2. Triggers\textsuperscript{5}  
   a. Variety of causes (Appendix A)
Figure 3. Interaction between airway inflammation and clinical symptoms and pathophysiology of asthma

3. Classification
   a. Mild, moderate, severe, and life threatening (Table 1)
   b. Status asthmaticus
      i. Differing definitions in the literature
      1. Respiratory failure or impending risk of respiratory failure secondary to severe asthma exacerbation
      2. Some use the term interchangeably with severe or life threatening asthma exacerbation
   c. Exacerbation classification determined by (Appendix B):
      i. Percent predicted FEV₁ or PEF
         1. Serial measurements at one hour intervals
         2. Only 65% of children 5 to 18 years old are able to perform lung function measurements
         3. Almost impossible to acquire from children < 5 years old
         4. Not indicated if initial assessment is a life-threatening asthma exacerbation
         5. Maneuvers may be very uncomfortable and difficult for patients with very severe exacerbations
         6. Do not delay therapy to obtain in exacerbation at any severity level
      ii. Signs and symptoms at presentation (see Appendix B for values)
         1. Pulse oximetry
            a. Indicated for FEV₁ or PEF < 40% predicted, patients in severe distress, or patients unable to perform lung function measures
         2. Respiratory rate
         3. Wheeze
            a. Use caution with assessment, may be unreliable
            b. Absence of wheeze may indicate severe obstruction
         4. Use of accessory muscles during respiration
         5. Heart rate
         6. Ability to speak
         7. Alertness
         8. Partial pressure of carbon dioxide (PCO₂)
         9. Arterial blood gas (ABG)
            a. Partial pressure of oxygen (PaO₂)
         10. Sign and symptom scores (Appendix E)
            a. Attempt to provide objectivity to severity assessment
            b. Particularly for those unable to complete objective lung function tests (FEV₁ or PEF)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Initial PEF (or FEV₁)</th>
<th>Symptoms and Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>≥ 70% predicted or personal best</td>
<td>Dyspnea only with activity</td>
</tr>
<tr>
<td>Moderate</td>
<td>40-69% predicted or personal best</td>
<td>Dyspnea interferes with or limits usual activity</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 40% predicted or personal best</td>
<td>Dyspnea at rest; interferes with conversation</td>
</tr>
<tr>
<td>Subset: Life threatening</td>
<td>&lt; 25% predicted or personal best</td>
<td>Too dyspneic to speak; perspiring</td>
</tr>
</tbody>
</table>
Management of Acute Asthma Exacerbation

1. Goals of therapy

2. Treatment (Appendices C and D)
   a. Combination therapy is standard of care
      i. Oxygen
      ii. Inhaled short-acting beta agonist (SABA)
      iii. Inhaled ipratropium
      iv. Systemic corticosteroids
   b. Mild to moderate exacerbations
      i. Oxygen to achieve oxygen saturation (\(\text{SaO}_2\)) \(\geq 90\%\)
      ii. Inhaled SABA every 20 minutes \(\times\) three doses in first hour
      iii. Oral systemic corticosteroids
   c. Severe
      i. Oxygen to achieve \(\text{SaO}_2\) \(\geq 90\%\)
      ii. High-dose inhaled SABA + ipratropium every 20 minutes or continuous for one hour
      iii. Oral systemic corticosteroids
   d. Life threatening
      i. Same as severe exacerbations, but use intravenous corticosteroids
      ii. May quickly deteriorate into respiratory failure (status asthmaticus)
         1. Consider adjunctive therapies
         2. Intubation and mechanical ventilation if necessary, do not delay

3. Monitoring and reassessment
   a. Follow FEV\(_1\) or PEF if available
      i. Otherwise, symptom driven assessment (Appendix B)
      ii. Good or incomplete response \(\rightarrow\) continue therapy
      iii. Poor response \(\rightarrow\) consider adjunct therapies
   b. Mild to moderate exacerbations
      i. Reassess after ~ one hour of therapy or three nebulized bronchodilators (Appendix C)
   c. Severe exacerbations
      i. Reassess after 20 minutes of therapy (one nebulized bronchodilator treatment)
   d. Life threatening exacerbations
      i. Bedside assessment, near constant

4. Intubation and mechanical ventilation
   a. Dangers of mechanical ventilation
      i. Exacerbation of air trapping/dynamic hyperinflation
         1. Barotrauma
         2. Pneumothorax
      ii. Hypotension
      iii. Ventilator-associated pneumonia
   b. Contradictory evidence for mortality differences
5. Adjunct therapy options
   a. Magnesium
      i. Smooth muscle relaxation and bronchodilation
      ii. Dose
          1. Adult: 2g IV
          2. Pediatric: 25-75mg/kg (max 2g)
   b. Heliox
      i. Low density helium may improve overall gas exchange
   c. Racemic epinephrine
      i. Vasoconstriction decreases airway edema, smooth muscle relaxation
      ii. Dose: one inhalation of 0.22mg epinephrine
         1. If symptoms do not improve, then may repeat one time
         2. After second dose, do not re-administer for three hours

Ketamine

1. Background
   a. Developed as an alternative intravenous (IV) anesthetic in 196511,12
      i. Structurally similar to phencyclidine (PCP)
   b. Characterized by a more rapid recovery time and less prominent emergence reactions compared to PCP
   c. Approved for use in 1970 in the US

2. Pharmacology
   a. Non-competitively binds to the PCP receptor in the N-methyl-D-aspartate (NMDA) channel
      i. Inhibits glutamate activation of the channel
      ii. Blocks excitatory signal12,14
      iii. Accounts for anesthetic, analgesic, and amnestic effects
   b. Adrenergic activity11,15
      i. Direct stimulation of noradrenergic neurons
      ii. Inhibits neuronal reuptake of catecholamines
      iii. Central and peripheral elevation of circulating concentrations
      iv. Stimulation of the sympathetic nervous system
   c. Anticholinergic activity11,15
      i. Inhibition of vagal pathways
      1. Direct relaxation of bronchial smooth muscle12,13
         a. Inhibits acetylcholine-induced increase in myofilament calcium sensitivity16
         b. Blocks L-type calcium channels in smooth muscle
   d. Racemic mixture of two enantiomers13
      i. S(+) enantiomer of ketamine
         1. Three - four times more potent affinity for the NMDA receptor, compared to R(-)
         2. May bind mu and kappa opioid receptors
            a. Hypothetical mechanism for analgesic effects
         3. Fewer side effects secondary to lower dose required for equipotent activity
      ii. R(-) enantiomer of ketamine
         1. Greater effect on airway smooth muscle relaxation

3. Pharmacokinetics and pharmacodynamics10
   a. Absorption
      i. Water and lipid soluble
      1. Poor oral bioavailability
   b. Distribution
      i. 47% protein binding
      ii. Initially distributes to highly vascularized tissue (e.g. heart, brain, lungs)
      iii. Volume of distribution: 2-3L/kg
      iv. Onset of action: 30 seconds
c. Metabolism
   i. Hepatic
   ii. Active metabolite: norketamine
   iii. Duration of action (IV): 5-10 minutes

d. Elimination
   i. Renal
   ii. Alpha half-life = 15 minutes
   iii. Beta half-life = 2.5 hours

4. Adverse effects
   a. Emergence reactions
      i. Hallucinations experienced as a patient emerges from anesthesia
      ii. Adults > children
         1. Reported incidence of emergence reactions in adults ranges from 0-30%
         2. Reported incidence of emergence reactions in children are 1.4%
      iii. Treatment: benzodiazepines
         1. Midazolam 0.05mg/kg IV, max 2mg
   b. Increased tracheal secretions
      i. Risk of aspiration
      ii. Consider pre-medication with an anticholinergic (atropine or glycopyrrolate)
   c. Laryngospasm
      i. Past reputation for increased risk for laryngospasm
      1. 0.02% of cases required intubation compared to 1.75% of cases with other agents
   d. Respiratory depression
      i. Ketamine does not suppress respiratory drive like other anesthetics
         1. Exception = when given as a rapid IV infusion
            a. Associated with rapid intravenous infusion or high-dose ketamine
               i. Always push over > 60 seconds to avoid respiratory depression
            b. Associated with single doses of ≥ 2.5mg/kg
            c. Associated with total doses of ≥ 5mg/kg
            d. More common in neonates
            e. Easily managed with bag-mask ventilation
      ii. Does not suppress the protective airway reflexes (coughing, sneezing, and swallowing)
         1. However, cases of transient apnea and aspiration have been reported

5. Pulmonary effects
   a. Observations in patients with asthma or reactive airway disease
      i. Ketamine caused an increase in pulmonary compliance and a decrease in airway resistance in intubated patients
   b. Two hypothesized mechanisms
      i. Central effect of ketamine-induced catecholamine release
         1. Stimulation of β2-adrenergic receptors → bronchodilation
      ii. Ketamine inhibition of vagal pathways
         1. Anticholinergic effects → direct relaxation of bronchial smooth muscle
Literature Review

1. Evidence for ketamine in intubated patients with bronchospasm
   a. Case reports

Table 2.

<table>
<thead>
<tr>
<th>Case 1 (28 year old)</th>
<th>Case 2 (35 year old)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-ketamine intervention</strong></td>
<td><strong>Patient status immediately prior to ketamine</strong></td>
</tr>
<tr>
<td>MV w/ PIP limited to 30cmH$_2$O</td>
<td>Agitated and PIP reaching 60-80cmH$_2$O*</td>
</tr>
<tr>
<td>Aminophylline 0.9mg/kg/hr IV</td>
<td>Neb-A</td>
</tr>
<tr>
<td>HCT 200mg Q6hr IV</td>
<td>Aminophylline IV</td>
</tr>
<tr>
<td>Neb-I 0.5mg Q4hr</td>
<td>HCT IV</td>
</tr>
<tr>
<td>Albuterol + inhaled isoflurane</td>
<td>Intubated</td>
</tr>
<tr>
<td>Intermittent NMB</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Ketamine therapy</strong></th>
<th><strong>Result</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5mg/kg/hr continuous IV</td>
<td>Within 6hr:</td>
</tr>
<tr>
<td></td>
<td>o Chest clear to auscultation</td>
</tr>
<tr>
<td></td>
<td>o Respiratory compliance improved</td>
</tr>
<tr>
<td></td>
<td>Within 26 hr:</td>
</tr>
<tr>
<td></td>
<td>o Successfully extubated</td>
</tr>
<tr>
<td></td>
<td>o Ketamine discontinued</td>
</tr>
<tr>
<td></td>
<td>o No recurrence of bronchospasm</td>
</tr>
<tr>
<td></td>
<td>PIP dropped to 40cmH$_2$O;</td>
</tr>
<tr>
<td></td>
<td>Extubated 3.25hr later</td>
</tr>
<tr>
<td></td>
<td>Uneventful recovery</td>
</tr>
</tbody>
</table>

| **Adverse effects** | **None** | **None** |

*Increased risk of pneumothorax is associated with PIP 35 – 50 cmH$_2$O; risk increases as pressures increase*).

Table 3.

<table>
<thead>
<tr>
<th>Author</th>
<th>(N)</th>
<th>Patients</th>
<th>Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirshman et al.</td>
<td>15</td>
<td>Dogs</td>
<td>Ketamine 10mg/kg IV, then 60mg IV Q15minutes</td>
<td>K alone: airway resistance did not increase significantly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intubated</td>
<td>Ketamine + propranolol 2mg/kg IV</td>
<td>Other 3 groups: airway resistance ↑ (p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Previously sensitized to Ascaris Ag</td>
<td>Thioptentine 15mg/kg IV, then 60mg IV Q15minutes</td>
<td>All: airway compliance ↓ (p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ketamine + propranolol</td>
<td>Suggests adrenergic &gt; anticholinergic ketamine activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Airway resistance measured before &amp; after Ag exposure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ketamine 1mg/kg IV bolus</td>
<td>Ketamine ↑PaO$_2$ (p&lt;0.05) and ↓ stethoscopic expiratory wheeze (p&lt;0.05) vs. placebo no signif change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>K alone: airway resistance did not increase significantly</td>
<td>Thoracic compliance unchanged</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ketamine 1mg/kg IV bolus</td>
<td>No adverse effects reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ketamine 1mg/kg IV bolus</td>
<td></td>
</tr>
<tr>
<td>Hemmingsen et al.</td>
<td>14</td>
<td>Intubated adults w/ bronchospasm</td>
<td>Ketamine 1mg/kg IV bolus</td>
<td>Ketamine ↑PaO$_2$ (p&lt;0.05) and ↓ stethoscopic expiratory wheeze (p&lt;0.05) vs. placebo no signif change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterogeneous intubation indications</td>
<td>K alone: airway resistance did not increase significantly</td>
<td>Thoracic compliance unchanged</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o 7/14 w/ hx of asthma</td>
<td>Other 3 groups: airway resistance ↑ (p&lt;0.05)</td>
<td>No adverse effects reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ketamine ↑ PaO$_2$ (p&lt;0.05) and dynamic compliance at 1, 8, and 24hr post ketamine (p&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ketamine ↑ PaO$_2$ and PIP at 1, 8, and 24hr (p&lt;0.01)</td>
<td>Adverse effects:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ PaCO$_2$ and dynamic compliance at 1, 8, and 24hr post ketamine (p&lt;0.01)</td>
<td>o 1 pt w/ tracheal secretions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ PaCO$_2$ and PIP at 1, 8, and 24hr (p&lt;0.01)</td>
<td>o 1 pt w/ hallucinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adverse effects:</td>
<td>o Neither d/c ketamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ketamine 2mg/kg bolus, then 20-60mcg/kg/min (1.2-3.6 mg/kg/hr)</td>
<td></td>
</tr>
<tr>
<td>Youssef-Ahmed et al.</td>
<td>17</td>
<td>Intubated children 5mo - 17yr w/ bronchospasm</td>
<td>Ketamine 2mg/kg bolus, then 20-60mcg/kg/min (1.2-3.6 mg/kg/hr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heterogeneous intubation indications</td>
<td>↑ PaO$_2$/FiO$_2$ and dynamic compliance at 1, 8, and 24hr post ketamine (p&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>o 11/17 for status asthmaticus</td>
<td>↓ PaCO$_2$ and PIP at 1, 8, and 24hr (p&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sedated with BZD &amp; paralyzed with NMB</td>
<td>Adverse effects:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o 1 pt w/ tracheal secretions</td>
<td>o 1 pt w/ hallucinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Neither d/c ketamine</td>
<td></td>
</tr>
</tbody>
</table>

MDZ = midazolam; BZD = benzodiazepines; NMB = neuromuscular blockers; PaO$_2$ = partial pressure of oxygen; FiO$_2$ = fraction of inspired oxygen; PCO$_2$ = partial pressure of carbon dioxide; PIP = peak inspiratory pressure; d/c = discontinuation; hx = history; Ag = antigen
Summary of evidence for ketamine in intubated patients

i. Ketamine improves bronchospasm in intubated patients as measured by:
   1. Airway resistance
   2. Airway compliance
   3. PaO₂ and PaCO₂
   4. PIP

ii. Adverse reactions were uncommon and manageable

Evidence for ketamine in asthma exacerbations for non-intubated patients

Pediatric case reports

Table 4.

<table>
<thead>
<tr>
<th>Case 1⁷</th>
<th>Case 2⁷</th>
<th>Case 3⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Severity of exacerbation (as defined in NHLBI)</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Pre-ketamine intervention</td>
<td>Multiple Neb-A, Neb-I</td>
<td>Neb-A and Neb-I x 3</td>
</tr>
<tr>
<td></td>
<td>Continuous Neb-A x 2.5hr</td>
<td>Continuous Neb-A</td>
</tr>
<tr>
<td></td>
<td>MP 2mg/kg IV</td>
<td>DXM 0.6mg/kg IV</td>
</tr>
<tr>
<td></td>
<td>Continuous HeO₂</td>
<td>Continuous HeO₂</td>
</tr>
<tr>
<td>Patient status immediately prior to ketamine</td>
<td>Worsening air exchange</td>
<td>Unimproved WOB</td>
</tr>
<tr>
<td></td>
<td>↑ dyspnea</td>
<td>Dyspnea</td>
</tr>
<tr>
<td></td>
<td>Accessory muscle use</td>
<td></td>
</tr>
<tr>
<td>Ketamine therapy</td>
<td>2mg/kg bolus, then 2mg/kg/hr + HeO₂</td>
<td>2mg/kg bolus over 2min, then 2mg/kg/hr</td>
</tr>
<tr>
<td>Result</td>
<td>Prompt improvement in dyspnea, WOB, and air exchange x hrs</td>
<td>Prompt improvement in RR, WOB, and air exchange x hrs</td>
</tr>
<tr>
<td></td>
<td>Then WOB ↑ so ketamine rate ↑ to 3mg/kg/hr → improvement</td>
<td>Then symptoms ↑ so ketamine rate ↑ to 3mg/kg/hr → improvement</td>
</tr>
<tr>
<td>Intubation required</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Occasional confusion</td>
<td>Occasional confusion</td>
</tr>
<tr>
<td></td>
<td>Mild nystagmus</td>
<td>Mild nystagmus</td>
</tr>
<tr>
<td></td>
<td>No hallucinations or agitation</td>
<td>No hallucinations or agitation</td>
</tr>
</tbody>
</table>

Neb-A = nebulized albuterol; Neb-I = nebulized ipratropium; MP = methylprednisolone; DXM = dexamethasone; HeO₂ = heliox (60% helium + 40% oxygen); Mg = magnesium sulfate; MDZ = midazolam; WOB = work of breathing; HR = heart rate; RR = respiratory rate
### Table 5.

#### Case 1

<table>
<thead>
<tr>
<th>Age</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of exacerbation (as defined in NHLBI)</td>
<td>Severe</td>
</tr>
</tbody>
</table>
| **Pre-ketamine intervention** | • Multiple albuterol MDI treatments @ home  
• Neb-A and Neb-I x 1 in ED  
• Continuous Neb-A 20mg/hr x 45 min  
• Epinephrine 0.3mg IM x 1  
• DXM 20mg IV x 1  
• Mg 2g IV x 1 |
| **Patient status immediately prior to ketamine** | • Getting tired  
• RR decreasing  
• No improvement in air exchange |
| **Ketamine therapy** | • 0.75mg/kg IV push  
• 30 min later  
  o 2nd bolus 0.75mg/kg IV, then 0.15mg/kg/hr  
  o Given with continuous Neb-A x 2 hr |
| **Result** | • RR rate decreased  
• Air movement improved by auscultation  
• Audible wheezing  
• After dissociation x 10min, able to speak 3-4 words/breath  
• After 30min worsening SOB and declining pulse oximetry  
• Symptoms improved again after second bolus and maintained with drip |
| **Intubation required** | No |
| **Adverse effects** | None reported |

MDI = metered-dose inhaler; Neb-A = nebulized albuterol; Neb-I = nebulized ipratropium; DXM = dexamethasone; Mg = magnesium sulfate; RR = respiratory rate; SOB = shortness of breath
b. Review of published retrospective and prospective studies

i. Pediatrics


| Background | • The CAS is a modification of that published by Wood et al.14
|            | o Severe asthma = CAS > 12; maximum CAS score = 23
| Objective  | • To evaluate effect of ketamine added to standard therapy in pediatric status asthmaticus
| Study design | • Prospective, observational, single-arm pilot study in two pediatric EDs over three months
|            | • Primary outcome: change in modified CAS
|            | • All patients received standard therapy (Neb-A and 2mg/kg IV MP) prior to enrollment
|            | • Intervention: 1mg/kg ketamine IV over 15 minutes, then 0.75mg/kg/hr for one hour and continuous Neb-A (10mg/hr for children; 15mg/hr for adolescents) + Neb-I x 1
|            | • Hallucinations/emergence reactions treated with MDZ 0.05mg/kg IV; ketamine d/c if persisted
|            | • Infusion rate was halved for HTN during the infusion; ketamine d/c if persisted >10min
| Patients | Inclusion criteria
|          | • Between ages 5 – 18
|          | • Hx/o asthma or reactive airway disease
|          | • Previous use of bronchodilators
|          | • Fulfill at least one of the following criteria:
|          | o CAS > 12 after initial tx
|          | o Initial PEF value ≤ 40% predicted
|          | o Three SABA w/o CAS improvement
|          | Exclusion criteria
|          | • Patient judged to be too ill by ED physician
|          | • Known allergy to ketamine
|          | • History of or current HTN
|          | • HTN defined as systolic or diastolic blood pressure ≥ 90th percentile for age
| Statistics | • ANOVA or ANOVA on ranks as appropriate, with correction for multiple comparisons
| Results | • n = 10 (5 males and 5 females); mean age 8 years (range 5-16yr)

<table>
<thead>
<tr>
<th>Time</th>
<th>Median CAS (range)</th>
<th>Mean RR (range)</th>
<th>Mean Percent Predicted PEF±SE (Range) (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediately prior to ketamine bolus</td>
<td>14.5 (8-21)</td>
<td>39 (26-58)</td>
<td>16 ± 10 (0-46)</td>
</tr>
<tr>
<td>Immediately after ketamine infusion complete</td>
<td>10.5 (4-12)*</td>
<td>30 (18-48)*</td>
<td>47 ± 14 (0-76)</td>
</tr>
<tr>
<td>One hour after ketamine infusion complete</td>
<td>9.5 (4-12)*</td>
<td>31 (17-42)*</td>
<td>69 ± 8 (53-95)**</td>
</tr>
</tbody>
</table>

* p < 0.001 compared to values prior to ketamine; ** p < 0.02 compared to PEF prior to ketamine

• Three patients did not complete the one-hour infusion
  o Persistent HTN (149/105); HTN resolved w/i 10 minutes discontinuation
  o Visual hallucinations 30 min after starting infusion; did not resolve after MDZ
  o Diffuse skin flushing 20 min after starting infusion; resolved after discontinuation
• One patient experienced visual hallucinations that resolved with MDZ and completed infusion

Author’s conclusions

• Initiation of ketamine in patients with severe asthma is associated with clinical improvement
• Side effects were easily managed with treatment or discontinuation of ketamine
• Ketamine is safe to use in non-intubated children

Critique

• Difficult to interpret and generalize a change in the CAS
• Did not explain point allocation or what was modified from the original 0-10 scoring system31
• Small sample size, no comparator arm
• Heterogeneous baseline therapy confounds results

Take home points

• Studied a severe exacerbation population, most had already failed continuous albuterol
• Bolus dose studied is < dose reported in case reports and < procedural sedation dose12
• High incidence of adverse effects (4/10)
  o The variety of adverse effects and small sample size make conclusions difficult

CAS = Clinical Asthma Score; ED = emergency department; PEF = peak expiratory flow; Neb-A = nebulized albuterol; Neb-I = nebulized ipratropium; MP = methylprednisolone; HTN = hypertension; SABA = short-acting beta; agonist; HR = heart rate; tx = therapy
<table>
<thead>
<tr>
<th>Background</th>
<th>• The PI is a clinical score validated in ED assessment of asthma in children(^\text{11}), (Appendix E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>• To evaluate effect of ketamine added to standard therapy in pediatric asthma exacerbations</td>
</tr>
<tr>
<td>Study design</td>
<td>• Prospective, single center, randomized, double-blind, placebo-controlled</td>
</tr>
<tr>
<td></td>
<td>• Primary outcome: improvement in PI score by 2 points</td>
</tr>
<tr>
<td></td>
<td>• All patients received standard therapy prior to enrollment: albuterol and ipratropium x 3 (nebulized or MDI) and steroid (2mg/kg oral PRED, 2mg/kg IV MP, or 0.4mg/kg IV DXM)</td>
</tr>
<tr>
<td></td>
<td>• Only the primary investigator assessed each patient and assigned the PI score</td>
</tr>
<tr>
<td></td>
<td>• Intervention: 0.2mg/kg IV ketamine bolus over 1-2 minutes, then 0.5mg/kg/hr for 2 hours or equal volume saline placebos for the same time increments + continuous Neb-A 10mg/hr</td>
</tr>
<tr>
<td></td>
<td>• Additional medications were withheld during the 2 hour ketamine infusion</td>
</tr>
<tr>
<td></td>
<td>• Patients could be removed from the study if:</td>
</tr>
<tr>
<td></td>
<td>o Patient deteriorated and required more aggressive therapy (per physician)</td>
</tr>
<tr>
<td></td>
<td>o Patient improved such that continuous Neb-A was not warranted (per physician)</td>
</tr>
<tr>
<td></td>
<td>o Adverse effects became intolerable</td>
</tr>
<tr>
<td></td>
<td>o Parents wished the study to be discontinued</td>
</tr>
<tr>
<td></td>
<td>• The primary investigator recorded his guess as to whether the patient received ketamine</td>
</tr>
<tr>
<td>Patients</td>
<td>Inclusion criteria</td>
</tr>
<tr>
<td></td>
<td>• Children ages 2 – 18 who present to ED with acute episode of wheezing</td>
</tr>
<tr>
<td></td>
<td>• Scored 8 to 14 on the PI after treatment with standard therapy</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>• Temperature &gt; 39°C (&gt;102°F) or focal infiltrate on CXR</td>
</tr>
<tr>
<td></td>
<td>• Use of steroids in previous 72 hours</td>
</tr>
<tr>
<td></td>
<td>• Allergy to ketamine</td>
</tr>
<tr>
<td></td>
<td>• Psychotic disorders, HTN, pregnancy, coexisting primary parenchymal pulmonary disease, coexisting congenital heart disease, or history of prematurity/bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>Statistics</td>
<td>• Last-value-carried-forward method was used for missing data points</td>
</tr>
<tr>
<td></td>
<td>• Student’s t-tests compare continuous variables; chi-square test for categorical variables</td>
</tr>
<tr>
<td>Results</td>
<td>• n=68 (ketamine = 33, placebo = 35); mean age was 6.1±4.0 years; 60% male</td>
</tr>
<tr>
<td></td>
<td>• Baseline PI score 10.3±1.1 placebo vs. 10.5±1.5 ketamine; difference 0.2 (95%CI, -0.5 to 0.8)</td>
</tr>
<tr>
<td></td>
<td>• 6 patients did not complete the infusion</td>
</tr>
<tr>
<td></td>
<td>o Ketamine: 2 improved and 2 deteriorated; Placebo: 1 improved and 1 deteriorated</td>
</tr>
<tr>
<td></td>
<td>• No significant difference between PI score at any time interval or decrease in PI score</td>
</tr>
<tr>
<td></td>
<td>• No patients were removed from the study due to adverse effects and or required intubation</td>
</tr>
<tr>
<td></td>
<td>• Primary investigator correctly guessed patient treatment in 37/58 patients (64%)</td>
</tr>
<tr>
<td>Author’s conclusions</td>
<td>• Ketamine did not provide benefit to standard therapy in children with moderately severe asthma exacerbation</td>
</tr>
<tr>
<td></td>
<td>• This dose of ketamine may not be high enough to provide effective bronchodilation</td>
</tr>
<tr>
<td></td>
<td>• The bronchodilation of continuous albuterol may be greater than that caused by ketamine</td>
</tr>
<tr>
<td>Critique</td>
<td>• Difficult to generalize a change in the PI, not widely used</td>
</tr>
<tr>
<td></td>
<td>• Single-center, single evaluator of primary outcome decreases generalizability of results</td>
</tr>
<tr>
<td>Take home points</td>
<td>• Ketamine did not benefit children with “moderately severe” asthma exacerbations</td>
</tr>
<tr>
<td></td>
<td>• No adverse effects/emergency reactions reported with 0.2mg/kg bolus of ketamine</td>
</tr>
<tr>
<td></td>
<td>o Correlates with lower overall incidence in children compared to adults</td>
</tr>
<tr>
<td></td>
<td>• May have better outcomes targeting a more severe exacerbation population that fails continuous albuterol or in whom intubation appears imminent</td>
</tr>
<tr>
<td></td>
<td>o Equal responsiveness among groups may have masked effect of ketamine therapy</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Objective</th>
<th>• To determine efficacy and safety of low-dose ketamine adjunct to conventional therapy for acute asthma exacerbations while avoiding dysphoric adverse effects</th>
</tr>
</thead>
</table>
| Study design | • Prospective, randomized, double-blind, placebo-controlled, single center  
  • Primary outcome: change in FEV₁  
  • All patients received standard therapy = O₂, bedside PEF, Neb-A Q20 min, and MP 125mg IV  
  • Intervention: all patients received continuous Neb-A 10mg/hr  
    o Original protocol: ketamine bolus 0.2mg/kg IV over 5 minutes, then 0.5mg/kg/hr x 3hr  
    o Phase 2 protocol: ketamine bolus 0.1mg/kg IV over 5 minutes, then 0.5mg/kg/hr x 3hr  
  • Questionnaire to assess patient and physician satisfaction with the treatment  
    o 1 (much worse than standard therapy) to 5 (much better than standard therapy) |
| Patients | Inclusion criteria  
• Adults between ages 18 – 65 with clinical diagnosis of asthma exacerbation  
• PEF < 40% predicted value after Neb-A 0.5mg Q20 minutes x 3  
Exclusion criteria  
• Need for emergency intubation  
• Inability to perform bedside spirometry  
• Known allergy to ketamine  
• Hypertension, CAD, hyperthyroidism, pregnancy, psychiatric disorder, history of COPD |
| Statistics | • Means and variances of interval data compared using a Student’s t-test  
• Frequencies of nominal data compared using a χ² test with Yates correction  
• Continuous data with multiple measurements analyzed using a repeated-measure ANOVA  
• Post-hoc power analysis calculated to be 80% for an alpha = 0.05 to detect a 20% difference |
| Results | • n=53 total; n = 44 in phase 2 protocol (the data analyzed)  
• Three episodes of dysphoria were noted in the first nine patients → blinding was interrupted, all were in the ketamine group  
  o As a result, ketamine bolus decreased to 0.1mg/kg over 5 minutes  
  o First nine patients under the original protocol were removed from the data analysis  
• Baseline characteristic differences were not statistically significant  
  o Hours of symptoms numerically higher in the ketamine group (K 85 ± 117 vs. P 47 ± 46)  
  o Reported no statistically significant difference in competing alternate interventions such as theophylline or magnesium, however frequencies were not given  
• Both ketamine and placebo groups improved with statistical and clinical significance  
• No statistically significant difference between the two groups in any outcome measured  
• Trend toward more adverse events in ketamine group (dysphoric reactions and dizziness)  
  o 17.4% [95%CI, 4.95 – 38.8] vs. 4.8% [95%CI, 12.0 – 23.8] (p=0.1180)  
  o Patients in the ketamine group rated their satisfaction with the treatment regimen significantly better than the placebo group (K 4.3 ±0.6 vs. P 3.7 ± 1.2) (p=0.0285) |
| Author’s conclusions | • Ketamine at a low enough dose to avoid dysphoric reactions demonstrated no measurable increase in bronchodilatory effect compared to standard therapy  
• Ketamine associated with an ↑ in adverse reactions and hospitalizations and a ↓ in intubations, though none of these differences were statistically significant  
• Some patients reported a preference for ketamine therapy over standard therapy |
| Critique | • Change in protocol  
• Sample size small  
• Unclear if the post-hoc power analysis included or excluded the first 9 patients  
• Authors state “competing interventions” (e.g. magnesium, theophylline) were not statistically significant between groups, but do not report frequency or distribution among interventions |
Take home points

- Very low dose of ketamine used; likely not high enough to induce bronchodilation
  - This implies that an effective bolus dose is absolutely necessary for efficacy
- Incidence of emergence reactions, while higher than placebo, is still relatively low
  - 17.4% of 23 patients = 4 patients; though the high end of the confidence interval 38.8% would be 8 of 23 patients
  - Understanding other risk factors for emergence reactions could decrease incidence
- May have better outcomes targeting a more severe exacerbation population that fails continuous Neb-A
  - Equal responsiveness among groups may have masked effect of ketamine therapy

FEV₁ = forced expiratory volume in one second; O₂ = oxygen; PEF = peak expiratory flow; Neb-A = nebulized albuterol; MP = methylprednisolone; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease

Summary of the evidence 21-35

1. Patients studied
   a. Severe exacerbation, failed multiple therapies
      i. Case studies
      ii. Petrillo et al. showed improvement in CAS and respiratory rate after ketamine
   b. Moderate exacerbation, failed intermittent albuterol and corticosteroids
      i. Allen et al. showed no difference in outcomes adding ketamine to standard therapy in children
      ii. Howton et al. showed no difference in outcomes adding ketamine to standard therapy in adults

2. Dose
   a. Reported ketamine bolus dose ranged from 0.1mg/kg to 2mg/kg IV
   b. Reported ketamine continuous infusion rate ranged from 0.15 mg/kg/hr to 3mg/kg/hr
      i. Duration of infusion ranged from one to eight hours

3. Safety and adverse effects
   a. Non-intubated patients are able to maintain airway after ketamine administration at appropriate dose and rate
      i. No patients in case reports or studies experienced decreased respiratory drive
   b. Adverse reactions
      i. Hallucinations observed in adults > children
         1. Consistent with trend observed in all indications of ketamine
         ii. Single incidents of hypertension and flushing

Recommendations

1. Overview
   a. Severe, life threatening asthma exacerbations can lead to respiratory failure requiring mechanical ventilation
   b. Alternative therapies (e.g. ketamine) may be attempted to prevent the need for intubation and mechanical ventilation
   c. Ketamine can produce bronchodilation and relaxation of bronchial smooth muscle, but known side effects preclude use in all patients
      i. Incremental benefit observed beyond other adjunctive therapies

2. Considerations for patient selection
   a. Severe or life threatening asthma exacerbations
   b. Failed standard therapy
      i. Continuous albuterol and ipratropium
      ii. Oxygen
      iii. Systemic corticosteroids
   c. Failed alternative therapies with stronger bodies of evidence
      i. Intravenous magnesium sulfate
         1. Adults: 2g
         2. Children: 25-75mg/kg, max 2g
   d. Intubation appears imminent
      i. Patient is getting visibly tired/worsening respiratory muscle fatigue
      ii. Inability to speak
      iii. Altered mental status
      iv. PCO₂ ≥ 42mmHg
e. Adults vs. children
   i. Side effect profile is more attractive in children
      1. Less incidence of emergence reactions
   ii. Would still consider in adults in whom intubation appears imminent
3. Consideration of ketamine dosing
   a. Intermittent bolus dosing 0.5mg/kg IV
   b. No continuous infusion
      i. Howton et al. and Allen et al. suggest no benefit to continuous infusion
      ii. Practicality of timely acquisition of the drip from central pharmacy
   c. Give subsequent doses in 20 minute intervals if patient still meets severe exacerbation criteria
4. Considerations for management of hallucinations
   a. Consider non-pharmacologic management
   b. Midazolam 0.05mg/kg IV push (max 2mg)
5. Treatment algorithm
References

Appendices

**Appendix A: Agents and events that may trigger asthma**

<table>
<thead>
<tr>
<th>Category</th>
<th>Triggers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infection</td>
<td>Respiratory syncytial virus (RSV), rhinovirus, influenza, parainfluenza, <em>Mycoplasma pneumonia, Chlamydia</em></td>
</tr>
<tr>
<td>Allergens</td>
<td>Airborne pollens (grass, trees, weeds), house-dust mites, animal danders, cockroaches, fungal spores</td>
</tr>
<tr>
<td>Environment</td>
<td>Cold air, fog, ozone, sulfur dioxide, nitrogen dioxide, tobacco smoke, wood smoke</td>
</tr>
<tr>
<td>Emotions</td>
<td>Anxiety, stress, laughter</td>
</tr>
<tr>
<td>Exercise</td>
<td>Particularly in cold, dry climate</td>
</tr>
<tr>
<td>Drugs/preservatives</td>
<td>Aspirin, NSAIDs, sulfites, benzalkonium chloride, non-selective beta blockers</td>
</tr>
<tr>
<td>Occupational stimuli</td>
<td>Bakers (flour dust); farmers (hay mold); spice and enzyme workers; printers (arabic gum); chemical workers (azo dyes, anthraquinone, ethylenediamine, toluene diisocyanates, polyvinyl chloride); plastics, rubber, and wood workers (formaldehyde, western cedar, dimethylethanolamine, anhydrides)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Mild</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>While walking</td>
</tr>
<tr>
<td></td>
<td>Can lie down</td>
</tr>
<tr>
<td>Talks in</td>
<td>Sentences</td>
</tr>
<tr>
<td>Alertness</td>
<td>May be agitated</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
</tr>
</tbody>
</table>
| Respiratory rate       | Increased                     | Increased                              | Increased                               |<br>Normal rates of breathing in awake children<br>Age<br>&lt; 2 months &lt; 60/min<br>2-12 months &lt; 50/min<br>1-5 years &lt; 40/min<br>6-8 years &lt; 30/min |<br>Normal rate |<br>&lt; 60/min |<br>1-2 years &lt; 120/min |<br>2-8 years &lt; 110/min |<br>Sit upright |<br>Normal rate |<br>&lt; 60/min |<br>Patients &lt; 2 less than 100/mmHg |<br>Children 2-12 months &lt; 160/mmHg |<br>1-5 years &lt; 120/mmHg |<br>6-8 years &lt; 110/mmHg |<br>Children &lt; 8 &lt; 30/mmHg |<br>Adults &lt; 20/mmHg |<br>Sit upright |<br>Normal rate |<br>&lt; 60/min |<br>PaO₂: arterial oxygen pressure; PCO₂: partial pressure of carbon dioxide; PEF: peak expiratory flow; SaO₂: oxygen saturation<br>Note: the presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation. Many of these parameters have not been systematically studied, especially as they correlate with each other. Thus, they serve only as general guides. The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and followup.
Appendix C. Asthma exacerbation management algorithm

**FIGURE 5–6. MANAGEMENT OF ASTHMA EXACERBATIONS: EMERGENCY DEPARTMENT AND HOSPITAL-BASED CARE**

**Initial Assessment (see figures 5–1, 5–3)**
- Brief history, physical examination, auscultation, use of accessory muscles, heart rate, respiratory rate.
- PEF or FEV₁, oxygen saturation, and other tests as indicated

**FEV₁ or PEF ≥40% (Mild-to-Moderate)**
- Oxygen to achieve SaO₂ ≥90%
- Inhaled SABA by nebulizer or MDI with valved holding chamber, up to 3 doses in first hour
- Oral systemic corticosteroids if no immediate response or if patient recently took oral systemic corticosteroids

**FEV₁ or PEF <40% (Severe)**
- Oxygen to achieve SaO₂ ≥90%
- High-dose inhaled SABA plus ipratropium by nebulizer or MDI plus valved holding chamber, every 20 minutes or continuously for 1 hour
- Oral systemic corticosteroids

**Impending or Actual Respiratory Arrest**
- Intubation and mechanical ventilation with 100% oxygen
- Nebulized SABA and ipratropium
- Intravenous corticosteroids
- Consider adjunct therapies

**Admit to Hospital Intensive Care**
(see box below)

**Repeat Assessment**
- Symptoms, physical examination, PEF, O₂ saturation, other tests as needed

**Moderate Exacerbation**
- FEV₁ or PEF 40–89% predicted/personal best
- Physical exam: moderate symptoms
- Inhaled SABA every 60 minutes
- Oral systemic corticosteroid
- Continue treatment 1–3 hours, provided there is improvement; make admission decision in <4 hours

**Severe Exacerbation**
- FEV₁ or PEF <40% predicted/personal best
- Physical exam: severe symptoms at rest, accessory muscle use, chest retraction
- History: high-risk patient
- No improvement after initial treatment
- Oxygen
- Nebulized SABA + ipratropium, hourly or continuous
- Oral systemic corticosteroids
- Consider adjunct therapies

**Good Response**
- FEV₁ or PEF ≥70%
- Response sustained 60 minutes after last treatment
- No distress
- Physical exam: normal

**Incomplete Response**
- FEV₁ or PEF 40–59%
- Mild-to-moderate symptoms
- Individualized decision re: hospitalization (see text)

**Discharge Home**
- Continue treatment with inhaled SABA.
- Continue course of oral systemic corticosteroid.
- Consider initiation of an ICS.
- Patient education
  - Review medications, including inhaler technique.
  - Review/Initiate action plan.
  - Recommend close medical followup.

**Admit to Hospital Ward**
- Oxygen
- Inhaled SABA
- Systemic (oral or intravenous) corticosteroid
- Consider adjunct therapies
- Monitor vital signs, FEV₁ or PEF, SaO₂
- Possible intubation and mechanical ventilation

**Poor Response**
- FEV₁ or PEF <40%
- PCO₂ >42 mm Hg
- Physical exam: symptoms severe, drowsiness, confusion

**Discharge Home**
- Continue treatment with inhaled SABAs.
- Continue course of oral systemic corticosteroid.
- Continue on ICS. For those not on long-term control therapy, consider initiation of an ICS.
- Patient education (e.g., review medications, including inhaler technique and, whenever possible, environmental control measures, review/Initiate action plan; recommend close medical followup).
- Before discharge, schedule followup appointment with primary care provider and/or asthma specialist in 1–4 weeks.

**Key:** FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; MDI, metered dose inhaler; PEF, peak expiratory flow; SABA, short-acting β₂-agonist; SaO₂, oxygen saturation
### Appendix D: Dosages of drugs used as standard therapy for asthma exacerbations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Child Dosage</th>
<th>Adult Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhaled short-acting beta₂-agonists (SABA)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td>Nebulizer solution (0.63mg/3mL; 1.25mg/3mL; 2.5mg/3mL; 5.0mg/mL)</td>
<td>0.15mg/kg (minimum 2.5mg/dose) Q20 min x 3 doses, then 0.15-0.3mg/kg up to 10mg Q1-4 hrs PRN, or 0.5mg/kg/hr continuous nebulization</td>
<td>2.5mg – 5mg Q20 min x 3 doses, then 2.5-10mg Q1-4hrs PRN, or 10-15mg/hr continuous nebulization</td>
</tr>
<tr>
<td></td>
<td>MDI (90mcg/puff)</td>
<td>4-8 puffs Q20 min x 3 doses, then Q1-4hr PRN</td>
<td>4-8 puffs Q20min up to 4 hours, then Q1-4 hours PRN</td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>Nebulizer solution (0.63mg/3mL; 1.25mg/0.5mL; 1.25mg/3mL)</td>
<td>0.075mg/kg (minimum 1.25mg/dose) Q20min x 3 doses, then 0.075-0.15mg/kg (up to 5mg) Q1-4hr PRN</td>
<td>1.25-2.5mg Q20min x 3 doses, then 1.25-5mg Q1-4hr PRN</td>
</tr>
<tr>
<td></td>
<td>MDI (45mcg/puff)</td>
<td>See albuterol MDI dose</td>
<td>See albuterol MDI dose</td>
</tr>
<tr>
<td><strong>Systemic (injected) beta₂-agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine 1:1,000 (1mg/mL)</td>
<td>0.01mg/kg (up to 0.3-0.5mg) subcut Q20min x 3 doses</td>
<td>0.3-0.5mg subcut Q20min x 3 doses</td>
<td>No proven advantage of systemic vs. aerosol therapy</td>
</tr>
<tr>
<td>Terbutaline (1mg/mL)</td>
<td>0.01mg/kg subcut Q20min x 3 doses, then Q2-6hr PRN</td>
<td>0.25mg subcut Q20min x 3 doses</td>
<td>No proven advantage of systemic vs. aerosol therapy</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>Nebulizer solution (0.25mg/mL)</td>
<td>0.25-0.5mg Q20min x 3 doses, then PRN</td>
<td>0.5mg Q20min x 3 doses, then PRN</td>
</tr>
<tr>
<td></td>
<td>MDI (18mcg/puff)</td>
<td>4-8 puffs Q20min PRN up to 3 hours</td>
<td>8 puffs Q20min PRN up to 3 hours</td>
</tr>
<tr>
<td><strong>Systemic corticosteroids</strong></td>
<td></td>
<td>(<strong>Applies to all three corticosteroids</strong>)</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>1-2mg/kg in 2 divided doses (max = 60mg/day) until PEF is 70% predicted or personal best</td>
<td>40-80mg/day in 1-2 divided doses until PEF is 70% predicted or personal best</td>
<td>For outpatient “burst,” use 40-60mg in single or 2 divided doses for total of 5-10 days in adults. Children use 1-2mg/kg/day, max 60mg/day, for 3-10 days.</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Prednisolone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Appendix E. Pulmonary Index

<table>
<thead>
<tr>
<th>Score</th>
<th>Respiratory rate</th>
<th>Wheezing*</th>
<th>Inspiratory-expiratory ratio</th>
<th>Accessory muscle use**</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; 30</td>
<td>None</td>
<td>5/2</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>31-45</td>
<td>Terminal expiration with stethoscope</td>
<td>5/3-5/4</td>
<td>±</td>
</tr>
<tr>
<td>2</td>
<td>46-60</td>
<td>Entire expiration with stethoscope</td>
<td>1/1</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 60</td>
<td>Inspiration and expiration without stethoscope</td>
<td>&lt;1/1</td>
<td>+++</td>
</tr>
</tbody>
</table>

* If no wheezing due to minimal air exchange, score = 3
** Accessory muscle use was scored by assessment of sternocleidomastoid activity; 0 = no apparent activity; ± = questionable increase; ++ = increase apparent; +++ = maximal activity