Status Asthmaticus in Children

_from ED to PICU_

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Status Asthmaticus

**DEFINITION:**
- A prolonged and severe asthma attack that does not respond to standard treatment.
- A life-threatening episode of Asthma that is refractory to usual treatment.
- A condition of progressively worsening bronchospasm and respiratory dysfunction due to asthma, which is unresponsive to *standard conventional therapy* and may progress to respiratory failure and the need for mechanical ventilation.

Epidemiology

- 6 million children <18 years of age:
  - The leading cause of chronic illness in children.
  - The leading cause of hospital admission for children <18 years.
  - Status asthmaticus remains a leading cause of PICU admission.
  - ~10 million missed school days and
  - $US 726 million lost because of missed work.
  - 470,000 (adults and children) annual hospital admissions.
  - ~5000 deaths/year, with 150–200 of those occurring in children <15 years of age.

Prevalence

- The prevalence of pediatric asthma in the US is increasing.

Morbidity

- The morbidity of pediatric asthma in the US is increasing.

Rate of self-reported asthma/1,000 population


Hospital discharge rates for asthma

MMWR 1996;45(17):350–33
Mortality
- Doubled between 1980 and 1995, but recently have stabilized.

Status Asthmaticus in Children
- **Pathophysiology**
  - Cytokines
  - Airway pathology
  - Autonomic nervous system
  - Pulmonary mechanics
  - Cardiopulmonary interactions
  - Metabolism

Pathophysiology
- **Asthma** is an inflammatory disease characterized by airflow obstruction due to airway hyperresponsiveness and bronchospasm and airway inflammation with mucosal edema and mucous plugging of the small airways.

Status asthmaticus: Pathophysiology
- **Inflammatory cytokines**
  - Airway inflammation is characterized by the submucosal cellular infiltrate of eosinophils, mast cells, and CD4 lymphocytes.
  - The presence of these cells correlates with disease severity.
  - The cascade of inflammation begins with degranulation of mast cells, usually in response to allergen exposure.
  - Activated mast cells and lymphocytes produce pro-inflammatory cytokines (histamine, leukotrienes, PAF), which are increased in asthmatics’

Mast Cell (Mastocyte)
- **Preformed mediators** (from the granules):
  - Histamine (2.5 pg/cell)
  - Proteoglycans, mainly heparin (active as anticoagulant)
  - Serine proteases
- **Newly formed lipid mediators** (eicosanoids):
  - Prostaglandin D2
  - Leukotriene C4
  - Cytokines
Early Phase

- Activated mast cells release histamine and leukotrienes, both activators of early airway smooth muscle spasm.
- The activated mast cells further activate T lymphocytes, which produce inflammatory cytokines (TH2) and IL-4, -5, and -13.
- In addition, chemokines (leukotriene B4) are released, which attract neutrophils and promote further activation of the proinflammatory cascade.

Late Phase

- Submucosal infiltration by eosinophils, neutrophils, and activated lymphocytes, is responsible for delayed bronchospasm.
- Early bronchospasm may be more sensitive to bronchodilating agents, while late bronchospasm is refractory to bronchodilation and more sensitive to anti-inflammatory therapy.
- This inflammatory environment results in overproduction of mucus; injury to airway epithelium that exposes nerve endings, which augments airway irritability; hyperresponsiveness; and mucosal edema.
- The final common pathway for the inflammatory cascade is bronchoconstriction and mechanical airway obstruction by edema and mucus.

Pathophysiology

- The autonomic nervous system also contributes to bronchoconstriction through parasympathetic activation of M3 receptors by acetylcholine.
- Excitatory nonadrenergic, noncholinergic pathways mediated by tachykinins.
- Similar parasympathetic pathways stimulate mucus production and concomitant airway obstruction.
Airway

- The irritable and inflamed airway is susceptible to obstruction triggered by
  - Allergens
  - Infections
  - Irritants including smoke
  - Exercise
  - Emotional stress
  - GE reflux
  - Drugs
  - Other factors

Lung mechanics

- Hyperinflation
  - Obstructed small airways cause premature airway closure, leading to air trapping and hyperinflation
- Hypoxemia
  - Non-homogeneous distribution of affected areas results in V/Q mismatch, mostly shunt

Pulmonary Mechanics and Gas Exchange Abnormalities

- Easier air entry during inspiration airflow obstruction during expiration, causing air trapping with each breath and lung hyperinflation
- With higher end-expiratory lung volumes, coupled with the fact that bronchospasm leads to increased airway resistance and reduced expiratory flow,
- Expiration becomes an active, rather than passive, process that results in high energy expenditure and substantial increased work of breathing (WOB)

Pulmonary Mechanics and Gas Exchange Abnormalities

- Diaphragmatic flattening from hyperinflation causes additional mechanical disadvantages for the muscles of expiration and additional energy expenditure.
- Both forced expiratory volume and forced vital capacity are decreased as a result of high airway resistance.
- Total lung volumes are increased because of increased functional residual capacity.

Flow Time Waveform

- Pulmonary Mechanics and Gas Exchange Abnormalities
  - Are due to V/Q mismatch, increased intrapulmonary shunt (atelectasis) and increased dead space (airway overdistension) that result from small airway obstruction due to mucus plugging, edema, and bronchoconstriction.
  - These initially manifest as hypoxemia and hypocarbia.
  - Atelectasis from small-airway obstruction causes areas of decreased ventilation but adequate pulmonary blood flow, and the resultant shunt leads to arterial hypoxemia.
  - As disease severity worsens, greater distal airway obstruction causes alveolar distention and increased pulmonary dead space.
Pulmonary Mechanics and Gas Exchange Abnormalities

- To compensate for this V/Q mismatch, **tachypnea** occurs.
- Despite increasing dead space to tidal volume ratio (Vd/Vt), **hypocarbia** persists because minute ventilation increases.
- Finally, intercostal and diaphragmatic muscles fatigue.
- Increased minute ventilation is unable to compensate for the greatly increased Vd/Vt ratio, and **hypercarbia** results. As fatigue worsens, progressive hypoxemia and hypercarbia ensue and result in **respiratory failure**.

Cardiopulmonary interactions

**Right ventricular load**
- high lung volumes stretch the pulmonary vasculature, increasing pulmonary vascular resistance and increasing right ventricular afterload, which may compromise right ventricular function.
- In addition, fluctuations in pleural pressures produce significant effects on the intrathoracic vessels and right atrial venous return

**Left ventricular load**
- During the large, negative intrathoracic pressure observed during inspiration, left ventricular afterload is increased and systolic blood pressure is decreased.
- Exaggerated variation in systolic blood pressure associated with intrathoracic pressure variation during inspiration is termed pulsus paradoxus.

**Pulsus paradoxus**
- P. paradoxus is the clinical correlate of cardiopulmonary interaction during asthma. It is defined as exaggeration of the normal inspiratory drop in systolic BP: normally < 5 mmHg, but > 10 mmHg in pulsus paradoxus.

**Cardiopulmonary interactions**

**Negative intrapleural pressure**

**Hyperinflation**

**Altered hemodynamics**

**Pulmonary edema**

**Pulsus paradoxus**

**Hypotension**

**Cardiopulmonary interactions**

**Pulsus paradoxus correlates with severity**
- All patients who presented with FEV₁ of < 20% (of their best FEV₁ while well) had pulsus paradoxus

**Metabolism**

- V/Q mismatch
- Hypoxia
- Increased work of breathing
- Dehydration
- Lactate
- Ketones
- Metabolic acidosis

**Assessment**

- Findings consistent with impending respiratory failure:
  - Altered level of consciousness
  - Inability to speak
  - Absent breath sounds
  - Central cyanosis
  - Diaphoresis
  - Inability to lie down
  - Marked pulsus paradoxus

**Risk factors for requiring ICU management**

- History of ICU admissions, mechanical ventilation or rapidly progressive or sudden respiratory deterioration
- Seizure or syncope during an asthma exacerbation
- Exacerbation precipitated by food
- Use of more than two beta agonist MDI canisters/month
- Insufficient or poor adherence to controller therapy
- Denial or failure to perceive the severity of illness
  - Not absolute indications for ICU admission
  - One third of children who die from asthma had no risk factors

**Severity Assessment**

- Peak Expiratory Flow Measurement: personal best
  - Moderate Attack: 40%–69%
  - Severe Attack < 40%

- Pulmonary Index Score

- Modified Pulmonary Index Score for Pediatrics

**Clinical Asthma Score**

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanosis or PaO₂</td>
<td>None</td>
<td>In air</td>
<td>In 40%</td>
</tr>
<tr>
<td>Inspiratory B/S</td>
<td>NI</td>
<td>Unequal or decreased</td>
<td>Absent</td>
</tr>
<tr>
<td>Expir wheezing</td>
<td>None</td>
<td>Moderate</td>
<td>Marked</td>
</tr>
<tr>
<td>Cerebral function</td>
<td>NI</td>
<td>Depressed or Agitated</td>
<td>Coma</td>
</tr>
</tbody>
</table>

**A Modified Pulmonary Index Score Predictive Value For Pediatric Asthma Exacerbations**

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse Oximetry</td>
<td>&gt;93% in RA</td>
<td>&lt;94% in RA</td>
<td>&lt;94% with 40% FiO₂</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>None</td>
<td>In RA</td>
<td>In 65% FiO₂</td>
</tr>
<tr>
<td>Inspiratory Breath Sounds</td>
<td>Normal</td>
<td>Unequal</td>
<td>Decreased to Absent</td>
</tr>
<tr>
<td>Accessory Muscles Used</td>
<td>None</td>
<td>Moderate</td>
<td>Maximal</td>
</tr>
<tr>
<td>Expiratory Wheezing</td>
<td>None</td>
<td>Moderate</td>
<td>Marked</td>
</tr>
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</tr>
</tbody>
</table>


The MPIS is highly reproducible and a valid indicator of severity of illness in children with asthma

Pediatric Chest Disease

Christopher L, Carroll, MD; Anand K, Sekaran, MD; Trudy Lerer, MD; Craig M, Schramm, MD; Connecticut Children’s Medical Center, Hartford, CT
A score of 7 or more should be admitted to ICU.

Chest X-Ray

- Not routinely indicated
- Exceptions:
  - Patient is intubated/ventilated
  - Suspected barotrauma
  - Suspected pneumonia
  - Other causes for wheezing are being suspected

### Staging

Based on ABG progressions in status asthma

**Stage 1:** Non hypoxemic, hyperventilating
- Low PCO2 and normal PO2.

**Stage 2:** Patients are hyperventilating & hypoxemic.
- Low PCO2 and low PO2

**Stage 3:** Normal PCO2 (due to respiratory muscle fatigue) Low PO2
- PCO2 is False Normal, serious sign of fatigue

**Stage 4:** Respiratory Failure
- PCO2 is high, PO2 is low, Very serious stage

### Approach to Severe Asthma

- Reverse bronchoconstriction
- Treat airway inflammation
- Correct hypoxemia
- Consider differential diagnosis
- Monitor for complications
  - Pneumothorax
  - Hypotension

### Status Asthmaticus in Children

#### Treatment

- **Conventional**
  - General, β-agonists, steroids, anticholinergics
- **Advanced**
  - Mechanical ventilation, ketamine, inhalational anesthetics
- **Unusual**
  - Theophylline, magnesium, LTRAs, heliox, bronchoscopy
  - ECMO, last resort

### Emergency Management in Anticipation of PICU Admission

- Focus upon the assessment of impending respiratory failure,
- Obtaining IV access/ fluids,
- Supplemental O2
- Continuous inhaled β-agonists,
- Ipratropium: Anticholinergic
- IV methylprednisolone.
- Some suggest that IV magnesium and/or IV β-agonists should be administered in the ED to aggressively treat severe status asthmaticus and prevent progression to the need for mechanical ventilation.
Oxygen

- Deliver high flow oxygen, as severe asthma causes V/Q mismatch (shunt)
- Oxygen will not suppress respiratory drive in children with asthma


Fluid

Judicious use of IV fluid necessary
- Most asthmatics are dehydrated on presentations - rehydrate to euvolemma
- Overhydration may lead to pulmonary edema
- SIADH may be common in severe asthma


PICU Management

General Care Issues

- Require IV access,
- Continuous cardiorespiratory monitoring,
- Continuous pulse oximetry.
- For spontaneously breathing children in the PICU, frequent blood gas monitoring is not required. Such children can usually be managed with close observation without indwelling arterial or central venous catheters
- For children who require mechanical ventilation, a Foley catheter and arterial and central venous access are required.

PICU Management

Fluids
- Supplemental Oxygen
- IV Corticosteroids
  - Hydrocortisone
    4-8 mg/kg x 1, then 2-4 mg/kg q 6°
  - Methylprednisolone
    2 mg/kg x1, then 0.5-1 mg/kg q 4-6°
- Inhaled β-agonists continuous
  - 15 mg/Hour 5-12 Kg
  - 15 mg/Hour 10-22 Kg
  - 20 mg/Hour > 20Kg

Inhaled β-Agonists

- β-receptor agonists stimulate β2-receptors on bronchial smooth muscle and mediate muscle relaxation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative R2 selective</th>
<th>Significant R1 cardiac effects</th>
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<tbody>
<tr>
<td>Terbutaline</td>
<td></td>
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<tr>
<td>Albuterol</td>
<td></td>
<td></td>
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<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoproterenol</td>
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</tbody>
</table>

Bisgaard H. J Asthma 1997;34(6):443

Inhaled β-Agonists

- Less than 10% of nebulized drug reach the lung under ideal conditions
- Drug delivery depends on
  - Breathing pattern
  - Tidal volume
  - Nebulizer type and gas flow
- Delivery of nebulized drug
  - Only particles between 0.8 – 3 μm are deposited in alveoli
  - Correct gas flow rate is crucial.
  - Most devices require 10-12 L/min gas flow to generate correct particle size
**Inhaled β-Agonists**
- Continuous nebulization is superior to intermittent nebulization
  - More rapid improvement
  - More cost effective
  - More patient friendly
  - Papo MC. Crit Care Med 1993;21:1479-86
  - Ackerman AD. Crit Care Med 1993;21:1422-4
- Continuous treatments have been shown to be safe in patients with underlying cardiac disease

**Steroids**
- Asthma is an inflammatory disease
- Steroids are a mandatory element of first line therapy regimen (few exceptions only)

**Anticholinergics - Ipratropium**
- Quaternary atropine derivative
- Not absorbed systemically
- Thus minimal cardiac effects
  - (But you will find a fixed/dilated pupil if the nebulizer mask slips over an eye!)
- Nebulize 250 - 500 μg every 4-6 hours
- Significant side effects
  - Hyperglycemia
  - Hypertension
  - Acute psychosis
  - Unusual or unusually severe infections
  - Steroids contraindicated with active or recent exposure to chickendoxics
  - Allergic reaction
  - Reported with methylprednisolone, hydrocortisone and prednisone

**Anticholinergics**
- Change in FEV₁ is significantly greater when ipratropium was added to β-agonists (199 adults)
  - Rebuck AS. Am J Med 1987;82:59
- Significant improvement in pulmonary function when ipratropium was added to albuterol (128 children)
- Sickest asthmatics experienced greatest improvement

**Next Step**
- IV B-agonists
  - Terbutaline
  - Epinephrine
  - Magnesium Sulfate
  - Theophylline
  - Leukotriene receptor antagonists (LTRAs)
  - Heliox
  - Sodium bicarbonate

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Kane GI. Am Pharmacist 1985;147(3):61-6
**β-Agonists**

**Intravenous β-Agonist**
- Consider for patients with severe airflow limitation who remain unresponsive to nebulized albuterol
- **Terbutaline** is i.v. β-agonist of choice in US
- Dosage: 0.1 - 10 μg/kg/min
- Small trial found a benefit of IV β-agonists in children
  
  
  **SIDE EFFECTS**
  - Tachycardia, agitation, tremors
  - Hypokalemia


**Magnesium**
- Smooth-muscle relaxation by inhibition of calcium uptake (= bronchodilator)
- Dosage recommendation: 25 - 75 mg/kg i.v. over 20 minutes

**Theophylline**
- Role in children with severe asthma remains controversial
- Narrow therapeutic range
- High risk of serious adverse effects
- Mechanism of effect in asthma remains unclear

**β-Agonists**

- Cardiac side effects
  - Myocardial ischemia known to occur with i.v. isoproterenol
  - No significant cardiovascular toxicity with i.v. terbutaline (prospective study in children with severe asthma)

  Chiarg VW. J Pediatr 2000;137(1):73-7
  - Tachycardia (and tremor) show tachyphylaxis, bronchodilation does not


**Magnesium**

- Several anecdotal reports
- Only one randomized pediatric trial
  - Randomized, placebo-controlled, blinded trial (n=31) in children with acute asthma in ER (MgSO₄ 25 mg/kg i.v. for 20 min)
  - Magnesium group had significantly greater improvement in FEV₁/PEFR/FVC
  - Magnesium group more likely to be discharged home
  - No adverse effects


**Theophylline**

- May have a role in selected, critically ill children with asthma unresponsive to conventional therapy:
  - Randomized, placebo-controlled, blinded trial (n=163) in children with severe status asthmaticus
  - Theophylline group had greater improvement in PFTs and O₂ saturations
  - No difference in length of PICU stay
  - Theophylline group had significantly more N/V

Leukotriene receptor antagonists (LTRAs)

- Asthmatic children have increased leukotriene levels (blood, urine) during an attack. Level falls as attack resolves
- LTRA administration is associated with improvement in lung function in asthmatics

- Steroid administration to asthmatics has little effect on leukotriene levels
- Thus, LTRAs may offer additional benefits to asthmatics on steroids

Intravenous LTRAs in moderate to severe asthma

- A single dose of i.v. montelukast (Singulair®) was associated with significant improvement in lung function compared to standard therapy

What is heliox?

- Helium/Oxygen mixture
- Laminar flow reduces the resistance associated turbulent airflow in more proximal airways
- Allows greater oxygen delivery during inspiration
- Reduced work of breathing

Helium - Oxygen (Heliox)

- Helium lowers gas density (if at least 60% helium fraction)
- Reduces resistance during turbulent flow
- Renders turbulent flow less likely to occur
- Helium-oxygen (80:20) decreased pulsus paradoxus and increased PEFR in a controlled trial of adult patients
- Heliox may worsen dynamic hyperinflation

Treatment of status asthmaticus in children: is there a place for sodium bicarbonate?

- Conclusion: pH < 7.15
- Sodium bicarbonate was administered in six patients. There was a significant decrease in pCO2 and an amelioration of the respiratory distress. No adverse effects were observed. Also since then no patient required intubation after admission to the PICU.
Non Invasive Ventilation

- BiPAP can reduce work of breathing, reduce bronchoconstriction and offset intrinsic PEEP
- Small trial used BiPAP in 30 patients with severe asthma after one neb in the ED
- Excluded patients with hypotension, Osat < 90%, depressed mental status, need for emergent intubation
- BiPAP was interrupted for short periods to deliver nebulized albuterol
- Significant improvement in PFTs


Next Step

- Mechanical Ventilation
  - Conventional Ventilation
  - High Frequency Oscillatory Ventilation
  - Inhaled Anesthetics
  - Ketamine
  - Sedation
  - Bronchoscopy / Bronchial lavage

Intubation, Ventilation

- Decision should be based on clinical deterioration
- Absolute indications:
  - Cardiac or respiratory arrest
  - Severe hypoxia
  - Rapid deterioration in mental state
  - Respiratory acidosis does not dictate intubation
- Neither hypoxia nor hypercarbia are absolute indications for intubation

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Why hesitate to intubate the asthmatic child?

- Tracheal foreign body aggravates bronchospasm
- Positive pressure ventilation increases risk of barotrauma and hypotension
  - > 50% of morbidity/mortality during severe asthma occurs during or immediately after intubation

Mechanical ventilation Conventional

- Positive pressure ventilation worsens hyperinflation/risk of barotrauma
- Thoughtful strategies include:
  - Pressure-limited ventilation, TV 8-12 ml/kg, short T1, rate 8-12/min (permissive hypercapnia)
    - Kacmarek RG. Pediatr Pulmonol 1991;11(2):120
  - Pressure support ventilation using PS=20-35 cmH2O (may decrease hyperinflation by allowing active exhalation)
    - Wetzel RC. Crit Care Med 1996;24(9):1603-5

When Conventional Mechanical Ventilation Fails

- HFOV (High Frequency Oscillatory Ventilation)
Ketamine

- Dissociative anesthetic with strong analgesic effect
- Ketamine is a bronchodilator, potentiates catecholamines
- Useful for induction (2 mg/kg i.v.) as well as continuous infusion (0.5 - 2 mg/kg/hr)
- Induces bronchorrhea, emergence reaction

Inhalational anesthetics

- Halothane, isoflurane have bronchodilating effect
- Halothane may cause hypotension, dysrhythmia
- Requires scavenging system, continuous gas analysis

Bronchoscopy, bronchial lavage

- Marked mucus plugging may render bronchodilating and anti-inflammatory therapy ineffective
- “Plastic bronchitis” has been described in asthmatic children
- Combined bronchoscopy/lavage has been used in desperately ill asthmatic children

When Every thing fails ECMO

- Extracorporeal Membrane Oxygenation Support
- When maximal medical therapy is failing, ECMO should be considered. Numerous case reports demonstrate high survival rates, even in a gravely ill patient population.
- The survival for children with refractory status asthmaticus who are placed on ECMO is ~90%.

Alternative and Experimental Agents

- Nebulized Furosemide, Lidocaine, Heparin
- Immune Modulator Therapy Methotrexate, Gold, Cyclosporin, Cholchicine, Hydroxychloroquine, Dapsone, Macrolide antibiotics, Anti-TNFa agents: etanercept and Infliximab
- IVIG

Questions