Treatment of Severe and Life-Threatening Status Asthmaticus in the Acute Care Setting: An Evidence Based Approach

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Asthma

- Most common chronic disease of childhood
  - 9.5% of children in the US
- More than 1 million ED visits per year
  - 1/4 children ages 0–4 with asthma visit the ED annually
- Current evidence clearly supports the use of inhaled bronchodilators and systemic steroids as first-line agents.
- In those who fail to respond to initial therapies, a variety of adjunct therapies and interventions are available with varying degrees of evidence to support their use

Akinbami 2011
Objectives

- To review current national guidelines for standard management of acute asthma
- To describe strategies for refractory “near-fatal” asthma including mechanical ventilation and adjunct therapies
This is not...

- Diagnosis
- Pathophysiology
- Long term management
- Asthma Severity Assessment
- Asthma Action Plans
- Prevention
Case Presentation

- 3 yo male with history of asthma presented to ED in respiratory arrest
  - HPI ~1 day URI sx. No previous admits for asthma
  - PE: Cyanotic, unresponsive, strong tachycardic pulse, undetectable SaO2
    - Difficult BVM with minimal air mvmt

Next steps?
Medications?
Ventilation strategies?
Asthma Pathophysiology... Simplified

- Airway narrowing
- Extensive plugging of airways with mucus and inflammatory infiltrates
- Hyperinflation
- Atelectasis
- Ventilation and perfusion mismatch
Characteristics of (Near–) Fatal Asthma

- Doubling of beta agonist usage in the previous month
  - Overdependence on beta agonists (>1–2 canister monthly)
- Current/recent use of glucocorticoids or not on ICS
- Frequent admissions (≥2/yr) or ED visits (≥3/yr)
- Admission to ICU or intubation
- Adolescents
- Non–Hispanic black
- Low socioeconomic status
- Illicit drug use
- History of psychiatric disease
- Difficulty recognizing severity of symptoms
- No written action plan
Standard approach

- **Work-up**
  - Vitals
  - Pulse ox
  - H&P
  - Blood gas
  - CXR

- **Therapy**
  - Oxygen
  - Beta-agonists
  - Ipratropium
  - Corticosteroids
**Blood gas**

- Routine use of ABG testing in all children with acute asthma is NOT justified
  - Pulse ox to evaluate oxygenation
- No set values for pH, PCO2, PO2 that are diagnostic for respiratory failure
- Do NOT be reassured by a normal blood gas
- In a child with severe, acute asthma, a rising PCO2 is worrisome and predictive of respiratory failure

Moses, Casati, Langhan, Kanis, Carruthers
Chest Xray

- Rarely affect patient management
- Usually abnormal: Hyperinflation, atelectasis
- Consider if:
  - Fever
  - Hypoxia
  - Focal abnormalities on exam
  - Not responding to treatment
  - No personal or family history of asthma
  - R/O foreign body, Pneumothorax, pneumomediastinum

Tsai, Roback, Mahabee-Gittens
Oxygen

- >90% of children with asthma exacerbations have a transient VQ mismatch and hypoxemia
  - Temporarily worse by inhaled β-agonist treatment
- Oxygen is recommended for most patients
- Guidelines:
  - >90–93% for severe exacerbations
  - >95% in children (GINA), pregnant women (NIH), patient’s with heart disease (NIH)

GINA 2014, NAEPP 2007
β2–agonists (Class IA)

- Firmly established as the standard first-line therapy in the treatment of children with asthma
- MDI with spacer: most cost effective & efficient
- Nebulized dose: 0.15–0.3 mg/kg/treatment
  - Max: 10 mg per treatment
- Evidence supports continuous therapy
  - 0.5 mg/kg/h (Max 20–45 mg/hr)
- Side effects: tremors, tachycardia, headache, hypokalemia
  - Clinical significance of hypokalemia?
- No evidence for IV or oral β2 agonists

NAEEP 2007, Sabato 2000
Xoponex

- R-enantiomer
- In vitro studies: S-enantiomer may have detrimental effects → tachycardia and jitteriness
- NIH: “Clinically comparable”
- No clinical benefit vs albuterol
  - No decrease in tremor, vomiting, palpitations, nervousness
  - No difference in hospitalization or ED length of stay
  - Higher cost
  - ? Modest decrease in tachycardia
    - ?Cardiac history

NAEPP 2007, Qureshi 2005, Rubin 2012
Ipratropium (Class IA)

- Anticholinergic
- Beneficial adjunct – ineffective monotherapy
- Acute setting only – no benefit to the addition of ipratropium in the inpatient setting
- Severe asthma (PEF <40% predicted)
  - Improves pulmonary function
  - Reduces hospitalizations
  - 1–3 doses during 1st hour of treatment
- Moderate asthma (PEF 40–70% predicted)
  - May reduce hospitalizations
  - May reduce length of ED treatment

NAEPP 2007
Systemic glucocorticoids (Class IA)

- “Recommended for all but the mildest cases”
- Reduced symptoms, hospitalizations, relapses
- Early use decreases hospitalization rates
  - Clinical effect begins within 4 hours
  - Triage nurse initiated corticosteroids
    - Time-series controlled trial (n=644)
    - Admission less likely (OR = 0.56, 95% CI: 0.36–0.87)
    - Improved time to steroid receipt (P<0.001)
    - Improved time to achieving mild status (P=0.04)
    - Improved time to discharge (P=0.02)
Systemic Glucocorticoids: Dose and Route

- PO preferred over IV
  - Equal efficacy (Class A Evidence)
  - Less invasive
- 1–2 mg/kg
- Max 40–60 mg
- Continue in hospital (Class A Evidence)
- Give supplemental doses to patients who take them regularly, even if exacerbation mild (Class D Evidence)

NAEPP 2007, Qureshi 2001
Systemic Glucocorticoids: Duration

- Recommendations between 3–10 days
- Noncompliance with 5 days is common
- Decadron (0.6 mg/kg)
  - 5d prednisone = dexamethasone (IM/IV x 1d, PO x 2d)
    - Decreased ED relapses and admissions 7–10 days post discharge
    - Significant cost savings
    - Decreased vomiting
    - Increased compliance

Inhaled corticosteroids

- Inadequate evidence to recommend their use alone in acute asthma (Evidence B)
- Early guidelines: double the dose of inhaled corticosteroid during asthma exacerbation
  - Not effective
- New evidence:
  - ICS initiated early in adults may obviate the need for systemic corticosteroids
    - 2 mg flunisolide/hr or 3mg fluticasone/hr x 3hr
    - Data in children inconsistent
    - Data suggestive but not yet enough evidence

Adjunct Therapies

- Magnesium
- Methylxanthines
- Leukotriene Modifiers
- Terbutaline
- Antibiotics
- Mucolytics
- CPT
- Isoproteronol
- Epinephrine
Magnesium

- Smooth-muscle relaxation and bronchodilator
  - Effect in 2 min after infusion, plateau 20–25 min, lasts 1–2 hours
- Meta-analysis:
  - Decrease hospital admissions (p=0.0006; NNT=4)
- May improve lung function with severe exacerbations
- Hypotension, flushing, changes in heart rate, muscle weakness

Magnesium

- NIH (Evidence B)
  - **Indicated** for children whose FEV1 fails to improve above 60% predicted after 1 hour of care

- Cochrane
  - No clinically important changes in all comers
  - Severe asthma
    - Improved FEV1 by 9.8% (95% CI: 3.8–15.8)
    - Admissions reduced (OR 0.10, 95% CI: 0.04–0.27)
  - **Safe and beneficial in severe acute asthma**
Inhaled Magnesium

- Decreased admission and improved pulm function?
- NIH: May be beneficial, more research needed
- Cochrane: 16 trials, n=896 (adults & kids)
  - Inhaled Mg vs albuterol
    - ?poor lung function, no improvement in admissions
  - Inhaled Mg plus albuterol
    - No improvement in pulmonary function (95% CI -0.27 to 0.74, n=188) or admissions (95% CI 0.49–1.16, n=249)
  - Inhaled Mg plus albuterol and atrovent
    - +improvement in pulm function
  - Possible benefit in severe asthma in addition to albuterol +/− atrovent

Blitz 2005, NAEPP 2007, Powell 2012
Methylxanthines

- Direct bronchodilator
- Immunomodulator, antiinflammatory effects
- Theophylline, aminophylline
- Cochrane: Methodological quality high
  - Improves FEV1 and PEF within 6 hrs
Methylxanthines

- NIH: Not recommended (Evidence A)
  - No apparent reduction in symptoms
  - Does not reduce number of treatments or LOS
  - Does not prevent intubation
  - Does not avoid ICU admission
  - May increase critical care unit length of stay and time to improvement
  - Vomiting, headache, abd pain, palpitations/arrhythmias, intractable seizures
  - Requires serum drug levels

Leukotriene modifiers

- Binds leukotriene in the lungs reducing bronchoconstriction and inflammation
- No role oral dose in acute asthma
- Adult study:
  - Significant improvement in FEV1 after IV Singular
  - Reduction in the risk of hospital admission
- Peds study:
  - No benefit, no improvement in FEV1

Terbutaline (β2 agonist)

- IV, SQ, nebulized
- Nebulized terbutaline not as good as nebulized albuterol
- Retrospective chart review (n=120)
  - Early administration of continuous IV terbutaline in the ED resulted in decrease in mechanical ventilation (16 vs 60%, p=0.001) over late administration

Doymaz 2014
Prospective, double blind, RCT pediatric acute severe asthma (n=49)
- PICU, continuous albuterol, not intubated
- Continuous IV terbutaline vs NS
- Terbutaline group →
  - Fewer hrs of albuterol (38 vs 52 hrs; p=0.073)
  - Shorter PICU LOS (13 hrs longer for placebo group; p=0.345)
  - None were statistically significant
  - Terbutaline group had 3 pts with elevated troponin
Terbutaline

- No GINA, NAEPP/NIH recommendations
- Cochrane
  - Beta2-agonists: IV vs nebulized
    - No evidence to support the use of IV β2-agonists alone. These drugs should be given by inhalation.
  - IV β2-agonists in addition to continuous nebulized β2-agonists
    - Limited evidence to suggest shorter recovery time and improved pulmonary index scores

Travers 2001, Travers 2012
Antibiotics

- NIH (Evidence B)
  - Antibiotics are generally **not recommended** for the treatment of acute asthma exacerbations
  - Unless...
    - Evidence for pneumonia
    - Strong suspicion of bacterial sinusitis
    - Fever and purulent sputum
Mucolytics

- NIH (Evidence C)
  - Avoid mucolytic agents (acetylcysteine, potassium iodide) because they may worsen cough and airflow obstruction
  - ?Pulmozyme, Atrovent
Chest Physiotherapy

- NIH (Evidence D)
  - CPT is not beneficial and unnecessarily stressful for breathless asthma patient
  - Further studies needed for ventilated patients
Isoproterenol (Evidence B)

- B–agonist
- NIH does not recommend use of IV isoproterenol in treatment of asthma because of the danger of myocardial ischemia in children
Epinephrine

- Paucity of literature
- Systemic (IV, IM, SQ) vs inhaled
- Beta agonist properties may result in bronchodilation
- Vasoconstriction may decrease mucus production
- Potential for excessive cardiac stimulation
Systemic Epinephrine Evidence

- Retrospective review adults with severe asthma
  - No efficacy data
  - Low rate of major and moderate rate of minor adverse events
    - SVT, CP with EKG changes, elevated troponin

- Randomized controlled crossover study:
  - SQ terbutaline demonstrated better improvement in RR, HR and wheezing than comparable epinephrine

- Prospective, RCT:
  - Sus–Phrine plus albuterol vs albuterol alone
  - No significant difference

Systemic Epinephrine

- **GINA**
  - SQ or IM *not indicated* for acute asthma

- **NIH**
  - Non-selective beta agonists including epinephrine are *not recommended* due to their potential for excessive cardiac stimulation
  - 1:1,000 0.01 mg/kg up to 0.3–0.5 q20 min x 3
  - No proven advantage of systemic therapy over aerosol
Nebulized Epinephrine Evidence

- Double blind, RCT of racemic epinephrine versus albuterol
  - No significant difference in pulmonary index score, length of stay, admission, or relapse
  - Epi group had significantly more minor side effects

- Meta-analysis of nebulized epinephrine versus β2 agonists in adults and kids
  - Nonsignificant improvement in Peak Flow and FEV1 compared to patients getting epi v salbutamol or terbutaline

Plint 2000, Rodrigo 2006
Interventions to Consider Prior to Intubation

- Ketamine
- NIPPV/BiPAP
- Heliox
Ketamine

- Bronchodilation and bronchorrhea
  - May aid in clearing mucus plugs
- Induction agent of choice in asthma
- Side effects: Laryngospasm, emergence phenomenon, lowers seizure threshold
Prospective observational study children with refractory acute asthma in the ED (N=10)

Loading dose of 1 mg/kg followed by 0.75 mg/kg/hr x 1 hr

1 hour post ketamine infusion:
- Clinical asthma score decreased from 14 to 9.5 (p<0.05)
- RR decreased from 39–30 (p<0.05)
Ketamine Evidence

- Double-blind, randomized, placebo-controlled trial
- 2–18 years with Pulmonary Index Score of 8–14 after 3 nebs/steroids (n=68)
- Loading dose 0.2 mg/kg followed by 0.5 mg/kg/hr infusion x 2 hr vs placebo along with continuous albuterol neb
- No significant difference in groups
  - Pulmonary Index Scores decreased by 3.2 in ketamine group and 3.6 in placebo group (95% CI – 0.4 to 1.3)

Allen 2005
Ketamine Evidence

- Case reports using ketamine successfully to avoid mechanical ventilation
- Case reports in pediatric ventilated status asthmaticus
  - Continuous infusion of ketamine (1.0–2.5 mg/kg/h) immediately improved airway obstruction
Ketamine (Class III)

- **Cochrane**
  - Only single study of non-intubated children
  - Did not show significant benefit
  - No review for adults
  - No studies available for intubated patients
  - Future study needed

- **NIH**
  - Despite theoretical benefits as premedication for intubation, clinical trials in non-intubated patients have not shown clinical benefit

Jat 2012, NAEPP 2007
BiPAP may facilitate administration of inhaled beta agonists
  ◦ Recruits small airways
May improve oxygenation, decrease WOB/fatigue
Safe, well tolerated
Requires cooperative patient with spontaneous respirations
No clear age cutoff
  ◦ One study ages 2–11 years
  ◦ Clear guidelines not yet established
May offer alternative to intubation
NIPPV Evidence

- Retrospective review (n= 83) of ED patients initially designated for admit to PICU
  - 88% tolerated
  - 77% decreased RR (by 24% on average)
  - 88% improved oxygenation (by 7% on average)
  - 10% rescued from PICU admit
  - No adverse events
NIPPV Evidence

- Retrospective analysis (n=165) of mod/sev asthmatics <20kg in PED
- Improvement in Pediatric Asthma Score (12.1 → 6.3)
- 5% patients discharged

Williams 2011
NIPPV Evidence

- Crossover study (n=20) in PICU
  - 1 intubated
  - 3 discontinued due to discomfort
- Clinical Asthma Score and Respiratory Rate improved in all patients
- Discontinuation of NIPPV associated with increased RR and CAS

Thill 2004
NIPPV Evidence

- Prospective, RCT (n=20) in PICU
- Standard care +/- NIPPV
- In NIPPV group:
  - Improvement in CAS improved at 2, 4–8, 12–16, and 24 hrs after initiation of interventions (P<0.01)
  - Improvement in RR (p=0.01)
  - Fewer children required adjunct therapy (11% v 50%, p=0.07)
  - No major adverse events
  - 9/10 tolerated NIPPV

Basnet 2012
NIPPV (Class III)

- **Cochrane**
  - Paucity of data
  - Suggestion of decreased need for intubation in adults
  - Meta-analysis not possible
  - No pediatric recommendations

- **NIH**
  - No recommendations

- **Possible additional benefit**
Heliox

- Mixture of helium and oxygen
- Promotes less-turbulent airflow through narrowed airways
- Increased laminar flow may reduce WOB and promote inhaled drug delivery
- May enhance diffusion effect on elimination of CO2
- Decreases auto-PEEP
- May prevent respiratory failure in children when used early
- Oxygen concentrations >30% significantly reduce the efficacy of heliox

Lee 2001
Heliox Evidence

- Much literature is anecdotal
- Controlled cohort of 2m–12y with mod–sev obstructive disease in the ED
- Nebs x 6 in Heliox (80:20) v O2 over 2 hours in ED (n=60)
  - 55% required more treatment in Heliox group v 95% in O2 group (p=0.034)
  - At 12 hr: 35% of Heliox group still requiring obs v 68% O2 group (p=0.02)

Braun Filho 2010, Lee 2005
Heliox Evidence

- RCT of Albuterol in Heliox v control (n=40)
- No statistically sig difference at 10–20 min with Heliox (p=0.169 and p=0.062)
- No statistically sig difference in admission rate
Heliox Evidence

- Study: RCT of 2–18 yrs with mod–sev asthma received nebs via 100% O2 v 70:30 Heliox
  - Change in Pulmonary index scores: Heliox 6.67 v O2 3.33 (p = <0.001)
  - Discharge: Heliox 73% v O2 33% (p = 0.05)

Kim 2005
Heliox Evidence

- Case series of pediatric ventilated patients
  - Addition of Heliox
    - Decreased PIP (40.5 to 35.3)
    - Increased pH (7.26 to 7.32)
    - Decreased CO2 (58.2–50.5)

Abd-Allah 2003
Heliox (Class IIIB)

- Cochrane Review
  - 10 trials (3 pediatrics)
  - Total 544 patients
  - No significant differences in admission or pulm function
  - Some improvement in pulm function only pts with the most severe pulmonary function impairment
  - Interpret with caution: “No role to play in initial treatment of patients with acute asthma”

- NIH:
  - Discrepancy in findings due to small sample sizes
  - “Consider heliox-driven albuterol nebulization for patients who have life-threatening exacerbations and for those patients whose exacerbation remain in the severe category after 1 hours of intensive conventional therapy”
Respiratory Failure

- Mechanical Ventilation
- Precedex
- Inhalational Anesthetics
- ECMO
Mechanical Ventilation: Indications

- Poor response to therapy
- Rising CO2 (PCO2 > 50)
- Severe hypoxia (PaO2 < 60)
- Waning mental status
- Impending respiratory arrest
- Cardiopulmonary arrest
Mechanical Ventilation

- **Avoid if possible:**
  - High risk of worsened hyperinflation, barotrauma & hypotension
  - ETT is noxious stimuli – worsens bronchospasm
  - Longer PICU duration and longer length of stay when adjusted for severity

- **Concerns:**
  - High lung inflation pressures
  - Auto–PEEP
  - Dynamic changes in lung compliance, airway resistance, VQ mismatch

Roberts 2002, Sabato 2000
Mechanical Ventilation Strategies

- No gold standard
- Cuffed ETT
- Anticipate hypotension
- Pressure vs Volume Modes
  - PCV has decelerating inspiratory flow
    - Ideal for short inspiratory time
    - Consistent MAP, requires less FiO2
  - PCV $\rightarrow$ decreased duration of ventilation (29 vs 24–52 hrs) and time to achieve normocarbia (5 vs 15–20 hrs)
  - Dual-control mode –
    - Pressure control with volume assured ventilation ideal?
- HFOV contraindicated due to dynamic air-trapping

Permissive Hypercapnia = controlled hypoventilation

- NIH Class C evidence
- Goal:
  - Adequate oxygenation and ventilation
  - Minimizing high airway pressures and barotrauma
- Hypercapnia due to increased physiologic dead space from hyperinflation
- No controlled studies comparing normocapnia with hypercapnia
- Underventilation agitates patients – generous sedation/muscle relaxation may be required

How high is too high?

- No consensus
- Animal studies: CO2 > 100 → decreased perfusion
- Increased intracranial pressure
  - Extreme = myocardial depression, cerebral hemorrhage, herniation, quadriplegia (> 120–135)
- Decreased cardiac contractile force
- Avoid with preexisting cerebral disease or myocardial dysfunction
- Keep PCO2 < 90–100 and pH > 7.15–7.2
  - May buffer with tromethamine

Mechanical Ventilation Strategies

- “Low and slow”
  - Low tidal volume: 5–6 mL/kg
  - RR = half normal for age
  - Minute ventilation ~100 mL/kg
- Goal plateau pressures <25–30
- Allow time for exhalation
  - I:E ratio = 1:3 or longer
- PEEP:
  - Initial PEEP = 0–3
  - Adjust PEEP to measured auto–PEEP
    - Expiratory hold maneuver
  - PEEP above auto–PEEP is not recommended

Mechanical ventilation monitoring

- Every attempt should be made to keep ventilator days to a minimum
- EtCO2 monitoring
  - EtCO2 does not reflect PaCO2 well in VQ mismatch
  - Capnogram
    - Assess severity of air trapping, eval bronchodilator therapy, guide appropriate ventilation parameters

Sabato 2000
Precedex (Dexmedetomidine)

- Selective alpha2–adrenoceptor agonist
- In vitro studies:
  - Smooth muscle relaxation and prevention of bronchoconstriction
- Animal studies:
  - Completely blocked histamine–induced bronchoconstriction in 5 dogs
- Case reports:
  - Facilitates induction of NPPV in adults

Groeben 2004, Takasaki 2009
Inhaled Anesthetics

- Airway smooth muscle relaxation
- Within 30 min
- Anecdotal case reports
- Practical limitations
- Safety:
  - Hypotension
  - Withdrawal/encephalopathy
  - Renal or hepatic injury

Inhaled Anesthetics

- Retrospective case series of 6 children with PIP >40
  - Isoflurane: ↓ PIP, ↑ pH, ↓ PaCO2
- Retrospective case series of 10 children with PIP >45, pH <7.25, PaCO2 >80
  - Improved minute ventilation, decreased peak pressures, shortened expiratory phase, improved PaCO2 (p=0.032) and pH (p=0.028)

Fig. 2 Arterial $\text{PCO}_2$ (in mmHg) before ($0\ h$) and $2\ h$ after ($2\ h$) initiation of isoflurane
Fig. 3 Arterial pH before (0 h) and 2 hours after (2 h) initiation of isoflurane
Inhaled Anesthetics

- Evidence?
  - Database review of >40 children’s hospitals 2004–2008
    - 3% of asthmatic pts requiring mechanical ventilation (n=47)
    - Longer lengths of stay, duration of ventilation, and higher hospital charges
    - No mortality benefit
  - Possible additional benefit above conventional therapy
Extracorporeal Life Support

- **Indication**
  - Severe refractory respiratory acidosis, hypercarbia

- **ECMO**
  - ELSO registry data 1986–2007
    - 64 children with severe refractory asthma
    - Ages 1–10, median PCO2 = 130, pH = 6.89
    - Survival = 83% –95%

- **Pumpless Extracorporeal Lung Assist**
- Risks hemolysis, post-decannulation thrombosis, sepsis, renal insufficiency, neurologic sequelae

Cutting Edge

- **Diagnosis/Predictive**
  - Exhaled nitric oxide in diagnosis
  - Urinary leukotriene E4

- **Treatment:**
  - Nebulized lidocaine
  - Nebulized Heparin
  - Nebulized TPA
  - Anti-IgE therapy with omalizumab
  - IVIG, hydroxychloroquine, colchicine, cyclosporin, methotrexate
  - Antifungal therapy
  - Complimentary and alternative treatments
Intubated after induction with Ketamine
Treated in ED with continuous albuterol, magnesium, solumedrol, and terbutaline
Initial blood gas: 6.80/110
Remained mechanically ventilated using permissive hypercapnia strategies in the PICU x 2 weeks on high dose continuous albuterol, magnesium, Precedex, ketamine, terbutaline, solumedrol

- Severe VQ mismatch – high need for FiO2
- Bacterial trachiiitis
Summary Guidelines

- O2 to relieve hypoxemia
- SABA for all patients (Evidence A)
- Inhaled ipratropium in severe exacerbations in ED (Evidence A)
- Systemic corticosteroids (Evidence A)
- Adjunct treatments (magnesium, heliox) merit consideration to decrease likelihood of intubation (Evidence B)
- Does not recommend methylxanthines, antibiotics, aggressive hydration, CPT, mucolytics, sedation, increased dosing of ICS
References:


References:


References:

40. Rowe BH, Bretzlaflf J, Bourdon C et al. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *Cochrane Database of Systematic Reviews* 2000, issue 1.
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References


Questions?