Best Practices in the ED Management of Status Asthmaticus

The management of status asthmaticus in the pediatric population can be challenged by controversies in the choice of novel therapies to treat severe asthma. In this session, the optimal management of status asthmaticus will be discussed for which evidence suggests best practices. Additionally, research in the comparative effectiveness of other therapies will be discussed.

OBJECTIVES

- Discuss first and second line therapy principles of management for status asthmaticus
- Describe the role of rescue therapies with NIPPV and HFNC in the management of severe asthma
- Discuss the role of heliox in improving work of breathing
- Describe pharmacological third line therapies: theophylline, IV beta agonists

3/26/2015
11:00 AM-11:45 AM
Grand Ballroom
TH-24

DISCLOSURES:
(+) No significant financial relationships to disclose

(+)**Charles Macias, MD, FACEP**
Associate Professor of Pediatrics, Section of Emergency Medicine, Baylor College of Medicine; Director, Evidence Based Outcomes Center and Center for Clinical Effectiveness, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas
Best practices in the ED management of status asthmaticus

ACEP Advanced PEM Assembly
March 26, 2015

Charles G. Macias MD, MPH
Chief Clinical Systems Integration Officer, Texas Children’s
Director, Evidence Based Outcomes Center and
Center for Clinical Effectiveness
Baylor College of Medicine
Texas Children’s Hospital
Houston, Texas

Overview

• To discuss existing evidence supporting diagnostic and treatment recommendations for acute severe asthma
• To delineate best treatment strategies for children experiencing acute severe asthma: comparative effectiveness of treatment strategies
• To describe the role of knowledge translation and quality improvement in severe acute asthma management in children: best practices
Scope of discussion

593,000 ED visits
2.3% of all ED visits in 2006
ED visits cost 5x PCP visits

Affects 22 million persons in the US (NHIS 2005)
10 million children in the US ever diagnosed (Vital Health Stat. 2009)

Mild: ≥70% predicted; dyspnea with activity; tachypnea
Moderate: 40-69% predicted; dyspnea interferes/limits activity
Severe: <40% pred; dyspnea at rest; LT: <25%; can’t speak; perspiring

Best practices in ED acute severe asthma

Domains of management

1. Airway edema: Treat inflammation
2. Airway smooth-muscle hypertrophy, hyperplasia, and bronchoconstriction: treat airway obstruction

Treat airway obstruction

2. AIRWAY HYPERRESPONSIVENESS

Inflammation

CLINICAL SYMPTOMS

AIRWAY OBSTRUCTION

3. Airway remodeling: coupled with above—maintain arterial oxygen saturation

Infants/children vs adults

• Infants/young children vs adults:
  - greater peripheral airway resistance
  - further extension of airway smooth muscle into the peripheral airways
  - less elastic recoil
  - disadvantage of the diaphragm

• Become hypoxemic more readily (VQ characteristics)
  - decreased SaO2 an early sign of severe airway obstruction
  - Sao2<92% RA 1hr after initial tx indicator of hospitalization for small infants (Connett and Lenney 1993; Geelhoed et al. 1994; Sole et al. 1999)

Vocal cord dysfunction (VCD)

• Consider in the difficult to treat
  - May also be induced by similar triggers
  - Abnormal VC adduction by indirect/direct visualization
  - Variable flattening of the inspiratory flow loop

• Elite athletes prone to EIB and VCD
  - Exercise related breathlessness

• Treatment: speech therapy and relaxation techniques
The goals have not changed:

- Adequate arterial oxygen saturation with supplemental oxygen
- Relief of airflow obstruction
- Reduction of airway inflammation

Airway smooth muscle mechanics

- Activates adenyl cyclase
- $\uparrow$ cellular cAMP
- Activation of PKA
- Inhibit myosin light chain kinase
- Inhibit intracellular Ca++ release
- Reduced Ca++ entry into cell
- Sequester intracellular Ca++
- Decreased contractility (smooth muscle relaxation)

G protein coupled receptors

$\beta_2$ agonist

$\beta_2$ AR

Parasympathetic tone

Anticholinergic

MgSO$_4$
Bronchodilators: beta agonists

1. Uncoupling
2. Sequestration
3. Downregulation

Expression of receptors

• Types of agonists
  - Full agonists
    • Isoproterenol
    • Epinephrine
  - Partial agonists
    • Albuterol
    • Terbutaline

• Number of receptors improves clinical efficacy
Continuous vs intermittent beta agonist

• Wide therapeutic index

• Data: limited trials
  - Dosing:
    • Pediatric trials: 15 mg/hour
    • NAEPP guidelines: 0.5mg/kg/hour
  - Few limit dosing to per/kg dosing making pediatric dose similar

Systematic review on continuous therapy:

• 165 RCTs

• Pulmonary function:
  - Continuous: significant improvements in PEFR, FEV1 and % Predicted FEV1
  - 2-3° improvements but not in 60”

• Secondary:
  - Decreased admission (RR 0.68; NNTT 10)
    • Pronounced in the higher severity group
  - Tolerability similar
  - No differences in side-effects

• Caution in extrapolating to young children

Camargo C Cochrane Database of Sys Rev 2003
GINA: Manage asthma exacerbations

- Repetitive administration of rapid-acting inhaled beta2 agonist
  - MDI with spacer is most cost effective and efficient
  - No evidence to support the use of IV beta2 agonists
  - Evidence supports the use of continuous therapy
  - Epinephrine- subcutaneous or IM not indicated for acute asthma

Levalbuterol: early data

- 482 patient 1-18 yrs
  - Faster improvement in levalbuterol
    - Difference in denominator (6 nebs)

Carl J Pediatr 2003
Levalbuterol: ED comparative effectiveness

- 129 children 2-14 yrs
- Moderate to severe
- No difference in clinical score or % change in baseline FEV1

Quereshi Annals of Emerg Med 2005

Levalbuterol continuous nebulization

- Double blind RCT 6-18 yrs
- 81 children failed ED therapy
- No difference in median time for continuous therapy or in adverse effects: HR and K+

Andrews et al. J Peds 2009
Levalbuterol

- ED based RCT 6-17yrs (n=99)
  - >FEV1 improvement and clinical score after 1 hour with 7.5mg of RAC
  - No differences in HR, RR, O2 saturation or admission rates

- Meta analysis: Cochrane
  - 7 trials, 1625 patients of all ages
  - Low to high quality of evidence
  - No difference in improvement measures (% change FEV1 and CAS), no difference in adverse effects (N/V, headache/jitteriness, nervousness/tremor)

- Pediatric cardiology patients (CHD, SVT, cardiomyopathy)
  - 192 patients (42 RAC, 40 levalbuterol, 10 both)
  - HR increase of approximately 6.5 beats per minute with equivalency in both groups

Wilkinson et al J Asthma 2011
Jat et al. Pulm Pharmacol Ther 2013
Kelly et al Ann Pharmacotherap 2013

Anticholinergic: ipratropium bromide

CNS

Blocks pulmonary muscarinic receptors

Pediatrics
Evidence for ipratropium

• RCT: acute severe (n=175)
  - 3 arms
  - ? hospitalizations
  Schuh et al, J Pediatr 1995

• Meta analysis
  - 20 trials, 2697 children
  - Most 3x 250mcg or 2x500mcg
  - Hospitalization: RR0.73
  - Overall NNTB: 16
  - Trends to greater effect with tx intensity/higher severity

Griffith Cochrane 2013
  - Plotnick Cochrane 2003
  NNTB:7 severe only

Ipratropium bromide

• Severe asthma:
  - Improves pulmonary function, CAS, SaO2
  - Reduces hospitalizations
  - 1 - 3 x 500 mcg doses during 1st hour of treatment
  - Variation in evidence/outcomes in ascertainment of groups (severity) and criterion standards for disposition

• No evidence for efficacy when used alone
**Systemic glucocorticosteroids**

- **Multiple equivalent regimens**
  - Oral prednisone/olone (1-2 mg/kg, max 40-60 mg) x 3-10d
  - Parenteral route equivalent to oral prednisone
    - IM dexamethasone acetate (n=32)
      - Gries et al, J Pediatr, 2000
    - IM dexamethasone acetate (0.6 mg/kg) (n=88)
      - Gordon et al, Pediatr Emerg Care, 2000
  - Oral dexamethasone (2 doses, 0.6 mg/kg) equivalent to 5 day prednisone
    - for outcome of unscheduled follow-up
      - Greenberg et al, Pediatrics, 2008
  - Meta-analysis of 6 ED RCTs to compare IM or oral dexamethasone to 5 day course of oral prednisone or prednisolone; patients receiving dexamethasone less likely to vomit (no difference in 5d relapse)
    - Keeney Pediatrics 2013
Systemic glucocorticosteroids

• Improving efficiency of care delivery
  - Evaluated the effect of early delivery (within 60 minutes) of triage
  - Early admission reduced odds of admission and length of treatment
  - Treatment with corticosteroids within 60 minutes decreased LOS by 25min
    Davis J Asthma, 2012

• Optimal use of steroids in severe asthma has yet to be determined
  - Effect of corticosteroids appears more pronounced in steroid naive and more severe
  - Early and consistent use of steroids, reserving IV for profound dyspnea, decreased LOC, intubated or in respiratory failure, vomiting

Knowledge translation: applying QI

• Strong evidence supporting early administration of systemic corticosteroids
  - Decreased LOS
  - Decreased hospitalization
  - Improved clinical scores
EC: Early Administration of steroids

- Expanding evidence-based practice
- Provider and staff inservicing
- Clinical decision support
- Bridging a continuum for home dose

Airway smooth muscle mechanics

- **β₂ agonist**
  - G protein coupled receptors
    - Activates adenylyl cyclase
      - ↑ cellular cAMP
      - Activation of PKA
        - Ca²⁺ dependent
          - K⁺ channels
        - Decreased contractility
          (smooth muscle relaxation)

- MgSO₄
  - Inhibit myosin light chain kinase
  - Inhibit intracellular Ca²⁺ release
  - Reduced Ca²⁺ entry into cell
  - Sequester intracellular Ca²⁺
**Magnesium sulfate**

- postulated mechanisms
  - modulates Ca^{2+} channel ion movement – direct effect on smooth muscle
  - inhibition of histamine release – airway anti-inflammatory effect

- IV bolus 25-100 mg/kg to 2 g (20 minute infusion)

- bronchodilatory effect in 2 minutes after infusion
  - plateau 20-25 minutes, lasts 1-2 hours

- untoward:
  - mild BP depression, flushing, tachycardia, bradycardia, muscle weakness

---

**IV Magnesium in children**

- Meta analysis of 5 RCTs with 182 children
  - Moderate to severe
  - Pulmonary function and clinical scores improved

_Cheuk Arch Dis Child 2005_
Magnesium

• Adult study of PEFR<50%: 1109 (≥6 years) at 34 UK hospitals
  - Randomized to IV magnesium, nebulized magnesium or placebo control
  - Weak support for IV on hospital admission outcome but none on PEFR or work of breathing
  - Concluded that nebulized magnesium was not more effective than placebo
    Goodacre *Health Technol Assess* 2014
  - Systematic review suggests IV magnesium reduces hospital admission (NNT=7)
    • Heterogeneity of ascertainment for “treatment failure” prior to magnesium
    Kew *Cochrane Database Syst Rev* 2014

Magnesium in adults and children

• Meta analysis of 16 studies of which 3 included pediatrics and 4 were exclusively pediatrics
  - No clear evidence nebulized magnesium improved pulmonary function or reduced admissions
  - When restricted to 3 trials, in those with severe asthma (FEV1<50%), possible improved lung function
    Powell *Cochrane Database Syst Rev* 2012

• Teasing out children from mixed populations seems to provide more evidence for improved pulmonary function and reduction of admissions with IV magnesium but not nebulized magnesium
  Shan *Respir Med* 2013
**Magnesium**

- **MAGNeSium Trial in children (nebulized)**
  - RCT with 3 doses of magnesium for 1 hour (151 mg)
  - 508 children 2-15
  - Assessment of the Yun Asthma Severity Score (ASS)
  - Small statistical gain in score with magnesium
  - Larger effect size with acute severe asthma with shorter duration of symptoms

  *Powell Health Technol Assess 2013*

- **Overall, no clear evidence in 20 years of data that magnesium produces significant side effects in children with acute asthma**

- **Stronger evidence for IV than nebulized, but even larger effect size for both IV and nebulized in children with severe acute asthma**

- **For children whose FEV1 fails to improve to >60% after 1 hour of care**

---

**Heliox**

- **Gas 7x lighter than air, combined with oxygen, a low density "air"**
  - Lowers the resistance to gas flow and turbulent flow
  - Potentially decreases the work of breathing by permitting an increase in ventilation

- **Perceived benefits**
  - Improved deposition of airway particles to the distal airways
  - Up to 50% more drug may be delivered

- **Delivery**
  - 11-16 L/min
  - 65:35 to 80:20 helium:oxygen
Heliox

• Reduction in clinical score and pulsus paradoxus by 10mm Hg (n=18)
• No change in pulmonary function or score (n=11)
  Carter et al. Chest 1996
• Continuous albuterol ± hi-flow Helium (240/20 min)
  • Improved pulmonary score using video assessment and trend towards
    reduced hospitalization (n=30)
    Kim et al. Pediatrics 2005
  • No change in clinical asthma score (n=41)
  • No change in clinical asthma score or LOS (n=42)
    Bigham et al. Pediatr Crit Care Med 2010

Heliox

• Meta analysis of 10 RCTs (3 with children)
  - Mean duration of treatment 120 minutes
  - Most use 70:30 mix of helium:oxygen
  - Improvement difference was 17.3% better for PEF % change with heliox vs oxygen
    • 17.2% mean difference with severe vs moderate-to-severe
  - Lower hospitalization rate (25 vs 36%)
  - Pediatric subgroup:
    • Decrease in clinical scores demonstrating decreased asthma severity
      Rodrigo Ann Allergy Asthma Immunol 2014
Ketamine

• Induction of bronchodilatation
  - Preventing reuptake of circulating catecholamines
  - Blocking calcium influx
  - Reduction of vagally mediated bronchoconstriction

• RCT in pediatric patients
  - 0.2 mg/kg bolus
  - Followed by 0.5 mg/kg/hr x 2 hrs
  - No difference in treatment arms

---

Pediatrics

**THE KITCHEN SINK**

---

**Pediatrics**
Aminophylline

• No apparent reduction in symptoms, number of txs or LOS
  Travers Cochrane Database Syst Rev 2005

Aminophylline

• Dosing/management practice patterns:
  - 6 mg/kg over 30 min followed by a maintenance dose of 1–1.2 mg/kg/h
  - Drug levels are obtained every 6 h during aminophylline infusion
  - Therapeutic level ≥ 10 mcg/ml
  - Toxic level 18

  Adapted from Dalabih Chest 2012

• Toxicity: vomiting*, tremor, headache

• Meta analysis including pediatrics studies demonstrate no benefit comparing IV beta(2) agonists versus IV aminophylline
  Mitra Cochrane Database Syst Rev 2012

Pediatrics
Terbutaline

• IV beta (2) agonist (partial agonist)

• Safety with some cases of elevated CKMB, hypokalemia, tachycardia and mild fall in DBP

• Retrospective chart review of 120 subjects admitted to PICU
  - 35 late start vs 85 early initiation: 60 vs 16% required mechanical ventilation
    Doymaz Ann Allergy Asthma Immunol 2014

Terbutaline

• Prospective: shortened PICU stays with standardized doses
  Carroll Pediatr Pulmonol 2006

• Double blind RCT of 49 children
  - Trend to improvement in clinical score over the first 24 hours
  - 38 vs 52 hours of continuous nebs for terbutaline vs placebo group
    Bogie Pediatr Emerg Care 2007

• TCH dose:
  - 0.5 mcg/kg/min continuous
  - increase by 0.5 mcg/kg/min
  - may require 3-6 mcg/kg/min
**NIPPV**: Bilevel positive airway pressure (BiPAP)

**Benefits**:
- May improve the delivery of bronchodilators to small airways
- Decreases workload/fatigue (decrease inspiratory muscle activity)

**Treatment to prevent hypercarbic and/or hypoxemic respiratory failure**

**Methods**:
- Inspiratory positive airway pressure max 20 cm H2O
- Expiratory positive airway pressure max 10 cm H2O
- Published cases in adults/children with sedation utilizing ketamine (mask intolerance)

**PED QI program**: 165 children ≤ 20 kg (lower range 7.5 kg and 7 months of age)
- 5% discharged from the ED, 2% intubated, 39% terminated BiPAP in ED
  
  Williams *Intensive Care Med* 2011

**Safe, well tolerated, improvement in clinical score**
- Prospective observational report of 72 PICU patients without control group
  - Decreased clinical score, HR, RR: intubation rate 4%
    
    Mayordomo-Colunga *Pediatr Pulmonol* 2011

  - Retrospective review (n=83)
    - 88% tolerated, 10% rescued from PICU admission
      

  - Unblinded RCT (n=20)
    - Improved clinical score and RR; only 11% (vs 50% of standard group) required adjunct therapies
      
      Basnet *Pediatr Crit Care Med* 2012
High Flow Nasal Cannula (HFNC)

- Allows >2L/min of flow through NC with control of temperature, humidity and O2 blend; provides indeterminate amount of positive airway pressure

- Retrospective cohort study of 498 cases in the PED (15% asthma)
  - Failure more likely with triage RR>90% age; PCO2>50mmHg; initial venous pH<7.3
    Kelly Pediatr Emerg Care 2013

- Retrospective review of HFNC for acute respiratory insufficiency in PED to PICU; utilizing an asthma subgroup
  - Infant/toddler flow max 7L/min; pediatric max 8L/min; adult max 50L/min
  - 87 patients when HFNC not available, intubation rate 5%
  - 99 patients when HFNC available, 9% use, 5% intubation rate
  - 172 patients when HFNC policy in place, 23% use, 0.6% intubation rate (p=0.03)
    Wing Pediatr Emerg Care 2012

Clinical standards

- Guidelines or pathways
  - Consistency of strategy for the patient
  - Common respiratory assessment score
  - Provide process to enhance efficiency for the providers
  - Engage stakeholders outside the division for smooth transitions
  - Allow analytics for understanding comparative effectiveness in your own setting
Clinical standards

• Improving outcomes
  - Common language throughout the system has allowed more rapid transfer
  - Reduced intubation rates
  - Decreased admission rates
  - Decreased LOS
  - Improved patient outcomes

Questions?