

New Therapies for Status Asthmaticus
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NAPNAP 2009, Session 305

Epidemiology:

- In 2005, nearly 9% of children (6.5 million children under age 18) were reported to have asthma
- In 2001, CDC introduced a more precise measurement of asthma and... from 2001-2005 the trend has remained stable at historically high levels
- Puerto Rican and non-Hispanic black children have the highest percentages of asthma (19.2 and 12.7)
- Among the 37 states (for which data were available) states with the *highest percentage* of childhood asthma were: Massachusetts, Hawaii, Oklahoma, Maryland, and Rhode Island. states with the *lowest percentage* of childhood asthma were: Utah, California, Iowa, Tennessee, and Washington.
- Nearly 4 million children missed school
cumulative total of 12.8 million lost school days due to asthma.
- Annual cost of >7.5 billion dollars/year
- Pediatric asthma-related ED visits remained fairly stable from 1992 to 2004 (103 visits per 10,000 children in 2004 compared with 97.6 visits per 10,000 in 1992).
- Asthma death rate under the age of 18
1999 = 3.0 deaths/1,000,000
2004 = 2.5 deaths per 1,000,000

Epidemiology – Research Findings:

- Childhood obesity increases PICU and hospital LOS
- Longer duration of O₂, continuous Albuterol, and IV steroids.
- Increased incidence in Hispanic patients with asthma exacerbation (Carroll, PCCM, 2006, 7(6): 527-31)

Risk Factors for Near Fatal Asthma:

Medical

Previous attack with rapid/severe deterioration
Previous ICU admissions with PaCO₂ >45 torr
Respiratory failure requiring mechanical ventilation
>2 β-agonist MDI's/month &/or poor escalation therapy

Psychosocial

Denial, non-compliance
Depression/psychiatric disorder
Dysfunctional family
Inner city resident

Sudden Asphyxial Asthma:

- Small subgroup
Typically adolescent males with poor med compliance
Usually no h/o NFA episodes
- H/O mild asthma who present acutely with sudden onset of severe airway obstruction resulting in cardiac arrest

Asthma Pathophysiology:

Asthma is characterized by diffuse lower airway obstruction resulting from:

- Airway inflammation and edema
- Bronchial smooth muscle spasm
- Mucus plugging

Triggers:

- Allergen exposure
- Respiratory tract infections
- Environmental irritants
 - Pollution
 - Second hand smoke
- Exercise
- Gastroesophageal reflux
- Drugs
- Emotional stress
- Household triggers

Inflammatory Cytokines:

Activated mast cells and lymphocytes produce pro-inflammatory cytokines (histamine, leukotrienes, PAF), which are increased in asthmatics' airways and bloodstream

Autonomic Nervous System:

Bronchodilation

- Sympathetic – circulating catecholamines stimulate β -receptors
- Parasympathetic – vagal signals stimulate bronchodilating M_2 -receptors
- Nonadrenergic noncholinergic (NANC) – release of bronchodilating neurotransmitters (VIP, NO)

Bronchoconstriction

- Parasympathetic – vagal signals stimulate bronchoconstricting M_2 -receptors
- Nonadrenergic noncholinergic (NANC) – release of tachykinins (substance P, neurokinin A)

Lung Mechanics:

Hyperinflation

- Obstructed small airways cause premature airway closure leading to air trapping and hyperinflation (increased FRC)

Hypoxemia

- Inhomogenous distribution of affected areas result in V/Q mismatch and shunting

Cardiopulmonary Interactions:

Left Ventricular Load

- Spontaneously breathing children with severe asthma have negative intrapleural pressure (can be as low as $-35 \text{ cmH}_2\text{O}$) during almost the entire respiratory cycle¹
- Negative intrapleural pressure causes increased LV afterload, leading to pulmonary edema²

Right Ventricular Load

- Hypoxic pulmonary vasoconstriction and lung hyperinflation lead to increased RV afterload¹

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 (> 10 mmHg)

Clinical Presentation:

Children with asthma can present with:

Cough

Wheezing

Audible wheezes = reasonable airflow

“Silent Chest” = ominous

Increased WOB

Anxiety

Restlessness

Oxygen desaturation

Assessment:

Findings c/w impending respiratory failure:

Inability to speak

Absent breathsounds

Diaphoresis

Inability to lie supine

Central cyanosis

Marked pulsus paradoxus

Altered level of consciousness

Severity of Asthma Exacerbation & Clinical Asthma Score by Woods:

(Wood DW. Am J Dis Child 1972;123(3):227-8)

Chest X-Ray:

Abnormalities

Hyperinflation secondary to air trapping

Peribronchial cuffing secondary to airway inflammation

Atelectasis secondary to mucus plugging

Infiltrate

Blood Gas:

Early phase of severe asthma

Hypoxemia results from VQ mismatch

Hypocarbica results from hyperventilation

Late phase

Hypercarbia develops with increasing airflow obstruction

Indication of impending respiratory failure

Decision to intubate should be based on the clinical assessment

Treatment Strategies:

- Close cardiorespiratory monitoring & neuro assessments
- Decrease stress level in the environment
 - Allow parents to remain if possible
 - Allow child to assume position of comfort
 - Provide supportive care for agitation and restlessness
- Sedatives should generally be avoided
 - Agitation/combateness is an important sign cerebral hypoxia**

IV Fluids:

Most asthmatics are dehydrated
rehydrate to euvolemia

Over-hydration should be avoided
May lead to pulmonary edema

Close glucose monitoring – may require insulin

Bicarbonate:

- Rx acidosis (pH <7.2)
- Acidosis antagonizes the effect of endogenous catecholamines and exogenously administered β -agonist therapy
- However CO₂ released with bicarb metabolism will lead to \uparrow hypercarbia
- Correction of acidosis results in an \uparrow in alveolar ventilation that offsets the \uparrow PaCO₂
- Dose: 1-2mEq/kg

Bicarbonate – Research Findings:

- CH Netherlands - PICU
- Retrospective study 1999
- 73 pts admitted in time period, 0.6-16.4yrs, fairly even gender split
- 17 pts with pH <7.15 with refractory status received 1-3 doses of standard dose bicarb
- Therapies included cont Alb nebs, atrovent, steroids, mag sulfate and required intubation
- Significant \downarrow in PCO₂ after bicarb & improvement in respiratory distress in all pt (Buysse, CHEST, 2005, 127(3): 866-870)

Oxygen:

- All asthmatic patients have ventilation/perfusion mismatch and thus require oxygen
- Oxygen should be delivered in the least invasive mode possible to decrease agitation
- Need for high flow should be differentiated from need for high FiO₂

Antibiotics:

- In general antibiotics are not a required part of the management strategy
- Need for antibiotics is patient-specific
 - ?Trigger
 - Exacerbations with non-infectious triggers do not require antibiotics
 - Most common infectious triggers are viral
 - ?Fever
 - ?Elevated WBC

Left shift vs. lymphocytosis
?Infiltrate on CXR

Beta Agonists:

- Crucial in asthma management
- Mediate bronchodilation via stimulation of beta 2 receptors on airway smooth muscle which, in turn, mediates smooth muscle relaxation
 - Beta 1 and beta 2 receptors are present in the lung with a ratio ~1:3
 - Epinephrine = significant β 1 (cardiovascular effects)
 - Terbutaline & Albuterol = β 2 selective

Beta Agonists – Research Findings:

- CH Michigan - PICU
- Retrospective study 2005
- 53pts(1.8-17.8yrs)
- Objectives: alert \uparrow WOB with met acidosis & hypervent rather than worsening airway
- Describe freq as 28%(n 15) developed met acid w/ hypervent (pH,7.35, PCO₂ <35, BE \leq -7, \uparrow lactate (n 4), gluc>120 (n 15)
- B-adrenergic agonist-induced lactic acidosis
- Met acid resolved contemporaneously with tapering of β -agonist therapy (Meert, PCCM, 2007, 8(6): 91-5)

Albuterol:

- Most commonly used beta agonist
 - B-receptor agonist (R-albuterol is active agent, S-albuterol is inactive)
- Dosing varies
 - Keep in mind that <10% of the medication nebulized actually reaches the lung*
- Safe at high doses
- Dose: 0.15mg/kg q 20min x3 then continuous at 0.3mg/kg/hr Hi of 5mg/kg/hr without cardiotoxicity *max 40mg/hr our unit
- Studies show 10mg/hr is safe, but need to monitor CPK
- Side effects – tachycardia, palpitations, muscle tremors, nervousness and anxiety, nausea, hypokalemia

Albuterol – Research Findings:

- Continuous nebulization superior to intermittent nebulization
 - More rapid improvement
 - More cost effective
 - More patient friendly
- (Papo, CCM,1993, 21:1479-86; Ackerman, CCM,1993,21:1422-4)

Albuterol vs. Levalbuterol (Xopenex):

- *Albuterol* a 50:50 mix of 2 molecules that are mirror images of each other, R-albuterol and S-albuterol
 - S-isomer associated with small \uparrow 's in bronchoconstrictive response to methacholine
- *Xopenex* is all R-albuterol responsible for bronchodilation
 - Therefore, smaller dose needed for therapeutic effect \downarrow side effects (tremors/tachycardia)

S/R-Albuterol (Albuterol)	R-Albuterol (Xopenex)
Onset neb/Max effect neb: 0.5-2hrs Duration: neb: 2-5hrs Metabolized in the liver to an inactive sulfate Half-life: 3.8hrs Excretion: 30% unchanged in urine Dose: 0.15-0.3mg/kg SNV Continuous nebulization: 0.5-3mg/kg/hr or 10-15mg/hr* Nebulized solution: 0.42% or 0.83%, (3ml) or 0.5% (0.5ml)	Onset neb: 10-17mins Max effect neb: 1.5hr Duration: neb: 5-6hrs Metabolized in the liver to an inactive sulfate Half-life: 3.3 -4hrs Excretion: 3-6% unchanged in urine Dose: 0.31 to 0.63mg SNV Continuous nebulization: ? Nebulized solution 0.31mg/3ml or 0.63mg/3ml

Albuterol vs Xopenex – Research Findings:

- In a randomized double-blind controlled study in 2000
- ED & ward in 1-8yr (n 482) nebulized Albuterol 1.25mg (n 278) vs Xopenex 2.5mg (n 269) q20mins (max 6 doses)
- Hospitalization was significantly lower in the Xopenex (43%) vs Albuterol (53%) group
- No change in LOS & no significant adverse events (Carl, J Pediatr, 2003, 143: 731-6)

Terbutaline:

- IV β 2-agonist
- Similar action as Albuterol
- If unable to adequately bronchodilate with nebulization
- Dose: continuous infusion titrated b/w 0.5 - 4mcg/kg/min
**Epinephrine infusion at bedside*
- Side effects: \uparrow HR, \downarrow BP, arrhythmias, tremors, h/a, nausea
- Follow: ST segments, CPK, \sqrt troponins if cardiac strain/injury (seen at high doses)

Terbutaline – Research Findings:

- Effective in patients with severe air flow limitation who remain unresponsive to nebulized albuterol
- Terbutaline is i.v. β -agonist of choice in US
- Dosage: 0.1-10 mcg/kg/min (Stephanopoulos, CCM 1998, 26(10):1744-8)

Terbutaline – Add'l Research Findings:

- In 49 pts ages 2-17yrs who failed acute asthma mgmt and were admitted to PICU were randomized into 2 groups
- One received IV Terbutaline vs IV NS while on cont Albuterol nebs
- CAS in the first 24 hours (T6.5 vs NS4.8), spent less time on continuous Albuterol (T38 vs NS52 hrs), and the NS group averaged 13 hrs longer in the PICU (Bogie, CCM, 2002, 30(2): 448-53)

Ipratropium Bromide (Atrovent):

- Anticholinergic
- Blocks the action of acetylcholine at parasympathetic sites in the bronchial smooth muscle, antagonizes cGMP-mediated bronchoconstriction, inhibits secretion from serous & seromucous glands lining the nasal mucosa
- Administer along with β -agonist
- Dose: 250-500mcg SVN q6h
- 15% reaches the lower airway
- Half life: 2 hrs
- Side effects: rare
-

Atrovent – Research Findings:

- Change in FEV₁ is significantly greater when Atrovent was added to β -agonists (n=199 adults), (Rebuck AS: Am J Med 1987;82:59)
- Highly significant improvement in pulmonary function when Atrovent was added to Albuterol (128 children) with sickest asthmatics experienced greatest improvement (Schuh S. J Pediatr 1995;126(4):639-45)

Atrovent – Add'l Research Findings:

- **ED** - Atrovent produces additional bronchodilation, resulting in fewer hospital admissions, particularly in patients who have severe airflow obstruction (Plotnick & Ducharme 2000; Rodrigo & Castro-Rodriguez, 2005).
- **Hospital:** Patients did not demonstrate a significant benefit from the addition of Atrovent to treatment after hospitalization for severe acute asthma (Craven et al. 2001; Goggin et al. 2001)

Steroids:

- Methylprednisolone (Solu-Medrol)
- ↓ inflammatory response, upregulate β -receptors
- **Mandatory element in 1st line therapy**
- Dose: 1-2mg/kg/dose IV q12h
is no known advantage for higher doses of corticosteroids in severe asthma exacerbations
- Side effects: glucose intolerance, hypokalemia, HTN, edema, Cushing's, etc

Magnesium Sulfate:

- Antagonize Ca⁺⁺ -mediated bronchoconstriction, promote smooth muscle relaxation and bronchodilation
- Duration of effect: varies by patient
- Dose: 25-75mg/kg IV (max dose 2g/dose)
- Some dose q6h but adding Mag Sulfate to IVF (1mg/ml)
*some advocate serum levels 4-6mg/dL
- Side effects: facial warmth/flushing, ↓BP, diarrhea, arrhythmias serum >6mg/dL
- Follow: serum Mg q6h

Magnesium – Research Findings:

- 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
(Ciarallo L. J Pediatr 1996;129(6):809-14)

Magnesium – Add'l Research Findings:

- CH RI – 2 ED's
 - Double blind placebo-controlled
 - 30 pts 6-18 yrs (16M/14P)
 - Mag sulfate 40mg/kg or NS
 - Pts who received mag had d/c home than those receiving NS
 - Outcomes;
 - Predicted PEFR
 - 20mins: 8.6% v 0.3%
 - 110mins 25.8% v. 1.9
 - FEV 1
 - 20mins 7.0% v. 0.2%
 - 110mins 24.1% v. 2.3
 - FVC
 - 20mins 7.3% v. 0.7%
 - 110mins 27.3% v. 2.6%
- (Ciarallo, Arch Ped Adol Med, 2000, 154: 979-83)

Methylxanthines (Theo/Aminophylline):

- Weak bronchodilator; may prevent diaphragmatic fatigue and upregulate β-receptors
- Dose (A): 6-8mg/kg IV load
- Continuous infusion:
 - 1mos-1yr: 0.2-0.9mg/kg/hr
 - 1-9yrs: 1mg/kg/hr
 - >9yrs: 0.8mg/kg/hr
- Serum level: 10-20mg/L
- Side effects: N/V, ↑HR, ↑BP, arrhythmias, sz, h/a, tremors
- Multi med interactions

Theophylline – Research Findings:

- 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 saturation
- No difference in length of PICU stay
- Theophylline group had significantly more N/V
(Yung M. Arch Dis Child 1998;79(5):405-10)

Theophylline – Add'l Research Findings:

- CH St. Louis – PICU
- Prospective randomized control (blinded) 1995-2000
- 47pts (13mos-17yrs); 6 pts req mech. Vent
- Theo associated with significant ↓ in time to reach CAS_{≤3}

41 not-intubated (20T/21C)

Theo 19hrs vs 31hrs

6 intubated (3T/3C)

Theo 66 vs 191 hrs

- Time to d/c criteria:

Not-intubated (Theo 30 vs 36hrs)

significant ↓ for intubated pt (Theo 75 ± 9hrs vs 189 + 34hrs)

- ↑incidence of emesis Theo ↑incidence tremors Control
- Theo safely improved recovery in pt who were also receiving cont alb, atrovent, steroids
(Ream, CHEST, 2001, 119:1480-88)

Theophylline vs Terbutaline – Research Findings:

- CH Cincinnati - PICU
- Controlled double blinded study
- Compared Theo vs Terb vs Theo & Terb mixed
- 40 pts (3-15yrs)
- No difference in asthma score, LOS, or adverse events *Hi incidence of nausea in group #3
- Group 1 median hosp cost of med & Theo levels was significantly lower (p<.0001)
- Theo when added to cont Alb + IV steroids is as effective as Terbutaline (Wheeler, PCCM, 2005, 6(2): 142-7)

Helium-Oxygen (Heliox):

- Less dense than nitrogen
- Flows at higher rates across narrowed airways with less turbulence
- Excellent delivery method for neb Albuterol
- Effective concentration: 80/20
- Effects become negligible at FiO₂>40% *if hi O₂ requirement d/t significant V/Q mismatch may not tolerate HO
- Modest ↓ in SaO₂ (85-90%) on HO may be tolerated if pt more comfortable & less distress
- Prevent entrainment of ambient air

Heliox – Research Findings:

- Anecdotal reports of improved respiratory mechanics in non-intubated and intubated asthmatic children
- Prospective, randomized, blinded cross-over study of heliox in non-intubated children with severe asthma (n=11) : no effect on respiratory mechanics or asthma score
(Carter ER. Chest 1996;109(5):1256-61)

Heliox & Albuterol – Research Findings:

- CH Pittsburgh – ED
- Randomized controlled, single blinded
- 30pts (2-18yrs) 15/15
- All PI ≥8
- All recv'd initial alb + O₂ + po steroids
- Randomized to HO 70/30 Alb or O₂ Alb cont neb

- Findings:
 Changed PI scores: HO Alb 6.67 vs O2 Alb 3.33
 d/c in <12hrs: HO Alb 73% (n 11) vs O2 Alb 33% (n 5)
- Cont Alb delivered by HO was associated with greater degree of clinical improvement
 (Kim, Pediatrics, 2005, 116(5): 1127-33)

Anesthesia:

- Anesthesia can provide sedation/bronchodilation when all other therapies maximized *but with risks
- Inhalant anesthetics: halothane & isoflurane
Halothane – 0.5-1.5% & O2 may produce prompt bronchodilation with rapid (15-20mins) PaCO₂ and pH improvement
 Side effects: hypotension, dysrhythmias, ↑V/Q mismatch
Isoflurane less side effects: hypotension *not arrhythmogenic
 After stable PaCO₂ and clinical obstruction is diminished (↓PIP) can wean

ECMO:

- Some case reports of successful use of ECMO
- 4 children (4, 10, 12,13yrs) successfully managed on pumpless arteriovenous
- ECMO circuit for CO₂ removal after marked progressive hypercapnia and acidosis on max therapy
- ECMO duration 18hr-5days, all survivors without complications Conrad, CCM, 2007, 35(11): 2624-64
- 2 adults cases also support the use of ECMO for CO₂ removal when therapy was maximized and continued progressive hypercapnia and severe acidosis (Elliot, CCM, 2007, 35(3): 945-48)

Intubation:

- +pressure applied to lungs that are hyperinflated with air trapping carries significant risk of barotrauma
- Should be reserved for pts with existing or impending resp failure
- 50% of morbidity/mortality during severe asthma occurs during or immediately after intubation
 (Zimmerman JL. CCM, 1993;21(11):1727-30)

Intubation Outside vs Pediatric Center:

- CH Connecticut –PICU
- Retrospective study 1997-2005
- (n 251) PICU; 130 peds ED & 116 community
- Community pts intubated 17% to 5% peds ED
- Community intubated sooner, required shorter intubation time & PICU days vs Peds ED or ICU intubated pts
- Although not significant Community pts received less vigorous pre-intubation therapies
 (Carroll, PCCM, 2007, 8(2): 519-23)

Rapid Sequence Intubation:

- Preoxygenate
- Avoid overzealous manual breaths

- Consider abd decompression
- Ketamine 1-2mg/kg IV
- +/- Midazolam (Versed) 0.1mg/kg IV (consider BP first)
- Rocuronium 1mg/kg IV or Vecuronium 0.1mg/kg IV

Immediately after Intubation – Be Alert for:

- Hypotension – circulatory decompression (consider volume administration)
- Consider pneumothorax if acute changes
- Consider ETT obstruction (secretions)

Ventilator Management:

- FiO₂ titrate to keep sats >88-90%
- PEEP 0-5 may stent open narrowed airways (cautiously add as pt has significant auto-PEEP)
- TV 6-10cc/kg titrated to maintain end-inspiratory plateau (PIP <35)
- Slow rate: lo-nl RR for age (prolonged expiratory phase causes long time constants that require extended time for exhalation)
- HO thru the vent if PIP hi/>35

Ventilation Therapies:

- Permissive hypercarbia (PCO₂ 60's)
- Controlled Hypoventilation
- Treat Metabolic Acidosis
- Sedation/muscle relaxants
- Lidocaine for suctioning
- Euvolemia and watch for SIADH

When to Extubate:

- Stable gases; PaCO₂ WNL on min vent settings
- NIF -25cmH₂O
- Alert, +gag & strong cough
- Extubate to cont nebs/HO
- Wean Terbutaline, Cont nebs and then titrate to q1h and overtime spacing
- Remember to begin long term therapies

Therapy Associated Complications

Airleak

Hyperinflation ± positive pressure creates predisposition for barotrauma

Prolonged Paralysis

Use of hi-dose steroids and chronic non-depolarizing muscle relaxants

Electrolyte disturbances

Hypokalemia, Hyperglycemia, Hypermagnesimias

Dysrhythmias

PVCs, myocardial ischemia

Pulmonary or Asthma-Allergy Consult

- helpful to get involved as patient begins to improve
- PCP communication throughout hospitalization to promote future management

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