

## Objectives

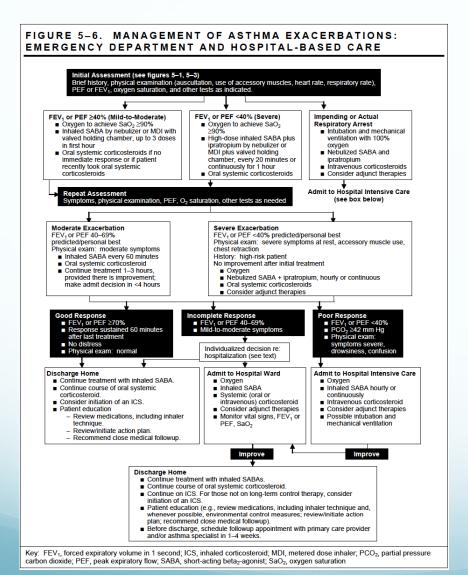
- Briefly review definitions of asthma events and seasonality of childhood asthma exacerbations
- Discuss initial therapy
- Discuss "adjunct therapies"

#### **Definitions**

- Asthma intermittent lower airway obstruction that is reversible either spontaneously or as the result of treatment
- Exacerbation a loss of asthma control that requires a change in usual asthma therapy
- Status asthmaticus a loss of asthma control that does not respond to changes in therapy that typically result in symptom control



## **Initial Therapy**



- Key points
  - Early, aggressive bronchodilator use
  - Early corticosteroid administration
  - Objective measure of airflow obstruction
  - Frequent reassessment

#### **Therapy Escalation**

First tier therapies: Inhaled β-2 agonist Inhaled anti-cholinergic Systemic corticosteroids

Level 1a Level 1a Level 1a

Second tier therapies: iv. magnesium loading

iv. aminophylline infusion iv. salbutamol infusion<sup>†</sup> Non-invasive ventilation

Heliox<sup>‡</sup>

Inhaled magnesium§

iv. magnesium continuous infusion

Level 1a
Level 1b
Level 2b
Level 2b
Level 2b

Level 4

Third tier therapies:

iv. ketamine infusion<sup>¶</sup> Inhaled anesthetics

**ECMO** 

Level 4 Level 4

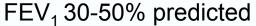
Level 4

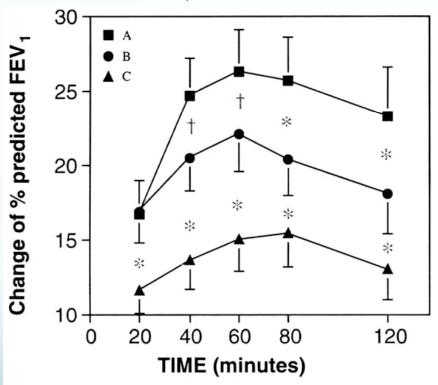
Intubation and mechanical ventilation if clinically indicated

#### Bronchodilators

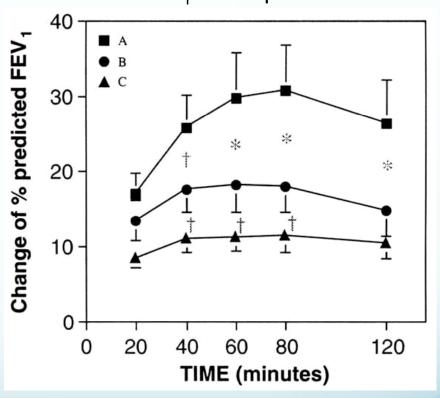
- High dose, selective β<sub>2</sub>-agonists preferred
- Initially every 20 minutes (or continuously) for the first hour
  - Onset of action <5 minutes</li>
  - Peak action 15-20 minutes
- Either nebulizer or MDI administration acceptable
- Anticholinergic should be added

## Inhaled Anticholinergic - Ipratropium





FEV<sub>1</sub> <30% predicted



A = 3 doses (N=40)

B = 1 dose (N=39)

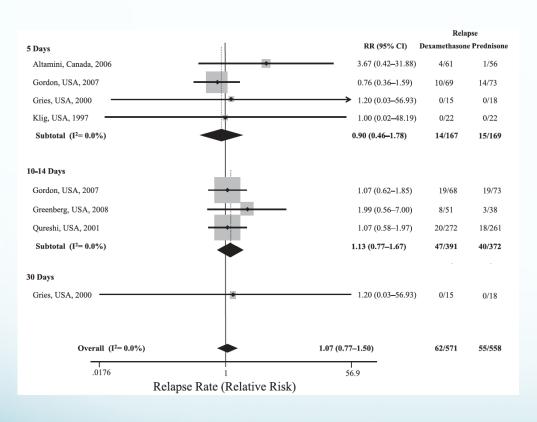
C = none (N=41)

Schuh S, et al. J Pediatr 1995; 126:639-645.

## Systemic Corticosteroids

- Give early and in sufficient doses
- Give as single daily dose or divided
- Oral dosing acceptable
- Prednisone, prednisolone, methylprednisone: 1-2 mg/kg/day for 3-5 days (or until PEFR >70% predicted/best)
- Dexamethasone 0.6 mg/kg/day

# Prednisone vs Dexamethasone



- Meta-analysis of 6 RCTs ED therapy
- 958 children (490 dex; 468 pred)
- No difference in relapse
- Slightly, but significantly less vomiting

Keeney, et al. Pediatrics 2014; 133:493-499.

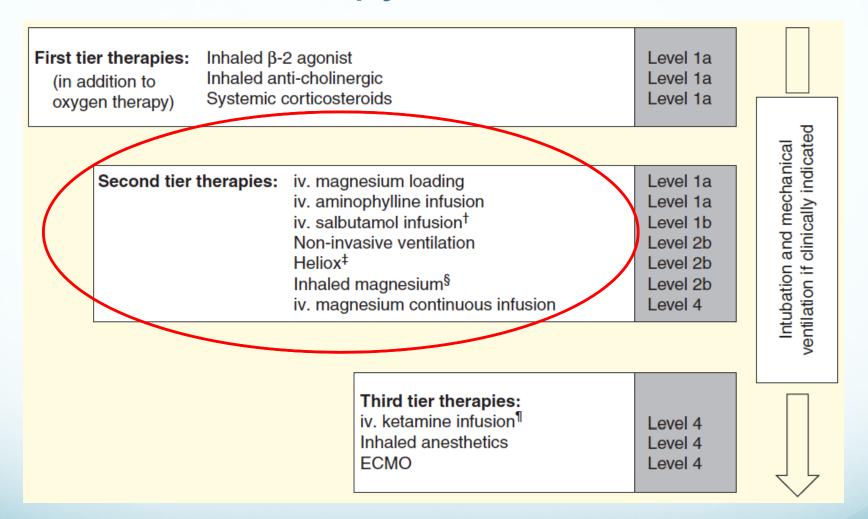
#### FIGURE 5-6. MANAGEMENT OF ASTHMA EXACERBATIONS: EMERGENCY DEPARTMENT AND HOSPITAL-BASED CARE Initial Assessment (see figures 5-1, 5-3) Brief history, physical examination (auscultation, use of accessory muscles, heart rate, respiratory rate), PEF or FEV<sub>1</sub>, oxygen saturation, and other tests as indicated. FEV<sub>4</sub> or PEF ≥40% (Mild-to-Moderate) FEV, or PEF <40% (Severe) Impending or Actual ■ Oxygen to achieve SaO<sub>2</sub> ≥90% Oxygen to achieve SaO<sub>2</sub> Respiratory Arrest Inhaled SABA by nebulizer or MDI with Intubation and mechanical valved holding chamber, up to 3 doses High-dose inhaled SABA plus ventilation with 100% ipratropium by nebulizer or in first hour oxvaen ■ Nebulized SABA and Oral systemic corticosteroids if no MDI plus valved holding ipratropium immediate response or if patient chamber, every 20 minutes or recently took oral systemic continuously for 1 hour intravenous corticosteroios corticosteroids Oral systemic corticosteroids Consider adjunct therapies Admit to Hospital Intensive Care Repeat Assessment (see box below) Symptoms, physical examination, PEF, O<sub>2</sub> saturation, other tests as needed Moderate Exacerbation Severe Exacerbation FEV<sub>1</sub> or PEF 40-69% FEV<sub>1</sub> or PEF <40% predicted/personal best predicted/personal best Physical exam: severe symptoms at rest, accessory muscle use, Physical exam: moderate symptoms chest retraction ■ Inhaled SABA every 60 minutes History: high-risk patient No improvement after initial treatment Oral systemic corticosteroid ■ Continue treatment 1–3 hours. Oxygen ■ Nebulized SABA + ipratropium, hourly or continuous provided there is improvement: make admit decision in <4 hours Grai systemic corticosier Consider adjunct therapies Incomplete Response ■ FEV<sub>1</sub> or PEF 40–69% FEV₁ or PEF ≥70% ■ FEV<sub>1</sub> or PEF <40%</p> ■ Mild-to-moderate symptoms PCO<sub>2</sub> ≥42 mm Hg Response sustained 60 minutes after last treatment Physical exam: No distress symptoms severe, Individualized decision re: ■ Physical exam: normal hospitalization (see text) Admit to Hospital Ward Admit to Hospital Intensive Care Discharge Home Continue treatment with inhaled SABA. Oxygen Oxygen ■ Continue course of oral systemic ■ Inhaled SABA Inhaled SABA hourly or corticosteroid. Systemic (oral or continuously Consider initiation of an ICS. intravenous) corticosteroid Intravenous corticosteroid Patient education Consider adjunct therapies Consider adjunct therapies Possible intubation and Review medications, including inhaler ■ Monitor vital signs, FEV, or technique PEF, SaO<sub>2</sub> mechanical ventilation Review/initiate action plan. Recommend close medical followup. Improve Improve 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: FEV<sub>1</sub>, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; MDI, metered dose inhaler; PCO<sub>2</sub>, partial pressure

carbon dioxide: PEF, peak expiratory flow: SABA, short-acting beta-agonist; SaO<sub>2</sub>, oxygen saturation

#### Key points

- Early, aggressive bronchodilator use
- Early corticosteroid administration
- Objective measure of airflow obstruction
- Frequent reassessment

#### **Therapy Escalation**



## Magnesium

- Multiple methods of action resulting in dose-dependent bronchodilatation
  - Decreases intracellular calcium
    - Facilitates uptake into sarcoplasmic reticulum
    - Inhibits slow inward calcium current
    - Impedes calcium-induced calcium release
  - Inhibits mast cell degranulation (histamine, PG)
  - Decreases acetylcholine release from motor nerve endings

## Magnesium

 Meta-analysis demonstrates decreased hospitalization following single dose 25-75 mg/kg IV over 20 minutes (NNT=4)

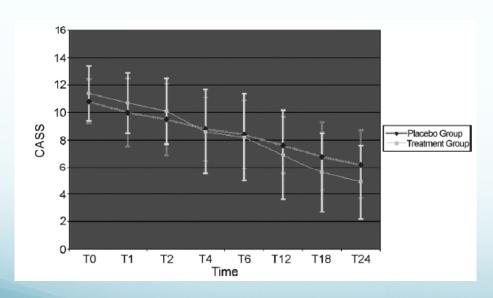
Citation	Effect name	Effect	Lower	Upper	Pvalue					
Ciarallo L, 2000	Hospitalisation	0.0345	0.0018	0.6756	0.0034		-	_		
Ciarallo L, 1996	Hospitalisation	0.0774	0.0038	1.5824	0.0437		-			
Devi PR, 1997	Hospitalisation	0.2350	0.0657	0.8414	0.0222			-		
Scarfone RJ, 2000	Hospitalisation	0.7404	0.2523	2.1729	0.5839			╼	_	
Combined (4)		0.2899	0.1426	0.5893	0.0006		-	-	I	
						0.01	0.1	1	10	100
						Fav	Favours treatment Fo		Favours placebo	)

Cheuk, et al. Arch Dis Child 2005; 90:74-77.

 Roles for continuous infusion or inhaled magnesium unclear - investigational

# Intravenous β-agonist

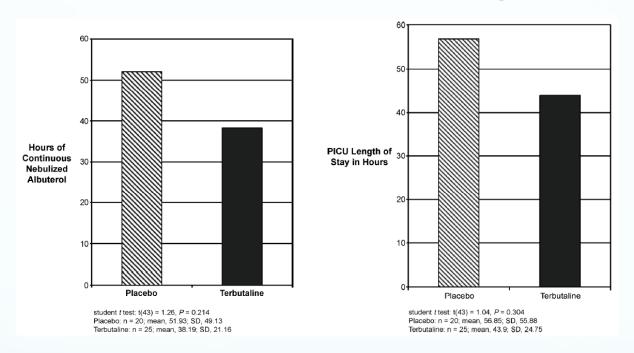
- Salbutamol frequently used world-wide
- Terbutaline used in US
- Evidence for efficacy of either is lacking.



- 49 children, 2-17 years
- non-intubated, receiving continuous inhaled albuterol
- placebo vs terbutaline (load 10 mcg/kg; 1-4 mcg/kg/min x 24 hours

Bogie, et al. Pediatr Emerg Care 2007; 23:355-361.

# Intravenous β-agonist



- Marginal and non-significant reductions in duration of continuous albuterol, PICU length of stay
- More adverse events in terbutaline group: 25% with elevated troponin; dysrhythmia (1 patient); chest pain with ST/T wave changes.
   Bogie, et al. Pediatr Emerg Care 2007; 23:355-361.
- Increased incidence of lactic acidosis in later studies.

## Intravenous Aminophylline

- Cochrane meta-analysis (Mitra, et al. 2005), compared to placebo:
  - Significantly improved FEV<sub>1</sub> 6-24 hrs
  - No difference in
    - Hospital length of stay
    - Frequency of nebulization therapy
    - Need for mechanical ventilation
- Must be monitored carefully
- Significant side-effect risk (vomiting most common)

#### Heliox

- Helium less dense than air
- Linear decrease in resistance to flow with increased concentration
- Decreases turbulence, further decreasing resistance
- Requires at least 60% helium to exert clinically significant effect
- Generally used in 70%:30% ratio

#### Heliox

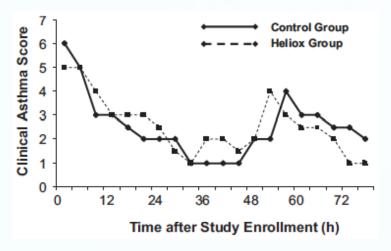


Table 3. Key study end points for heliox (n = 22) versus control (n = 20) study groups

	Heliox Group Mean ± SEM	Control Group Mean ± SEM	р
Time to hospital discharge eligibility, hrs	$66.2 \pm 8.7$	$63.4 \pm 8.6$	.614
Time to CAS <3, hrs	$22 \pm 2.7$	$21.2 \pm 5.3$	.273
CAS at 24 hrs	$2.9 \pm 0.3$	$2.4 \pm 0.6$	.172
CAS at study end	$1.6 \pm 0.4$	$1.6 \pm 0.4$	.876

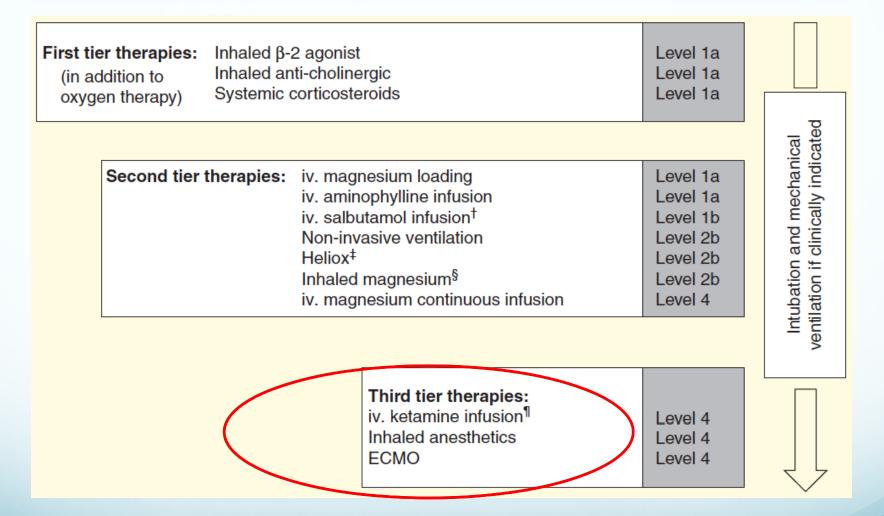
Table 4. PICU subgroup analysis of key study end points for heliox (n=17) versus control (n=17) study groups

	Heliox Group Mean ± SEM	Control Group Mean ± SEM	p
Time to hospital discharge eligibility, hrs	$74.0 \pm 9.0$	$65.8 \pm 9.1$	.242
Time to PICU discharge eligibility, hrs	$34.4 \pm 6.2$	$33.3 \pm 7.6$	.642
Time to CAS <3, hrs	$24.4 \pm 2.8$	$23.7 \pm 5.7$	.336
Duration of continuous gas administration, hrs	$25.6 \pm 4.6$	$24.33 \pm 5.8$	.514

- 42 children, 2-21 years
- Moderate-severe status asthmaticus
- Continuous albuterol driven by heliox (70%/30%)
- Excluded for FiO2 need >0.40
- No difference in any outcome
- No differences in adverse events

Bigham, et al. Pediatr Crit Care Med 2010; 11:356-361.

#### Therapy Escalation



## Ketamine

- Low level of evidence to support its use, primarily in intubated children
- Utility limited by
  - Need for concomitant use of sedation (benzodiazepines)
  - Potent secretagogue

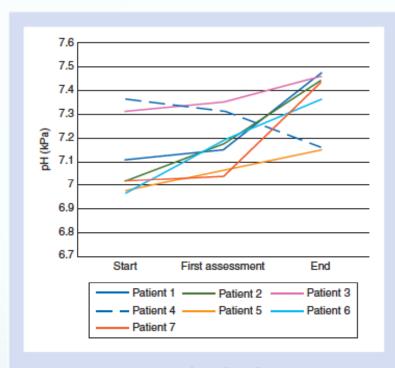


Fig 1 pH values per patient before, after a first assessment, and at the end of treatment with sevoflurane. The dashed line shows the patient who did not respond to sevoflurane therapy.

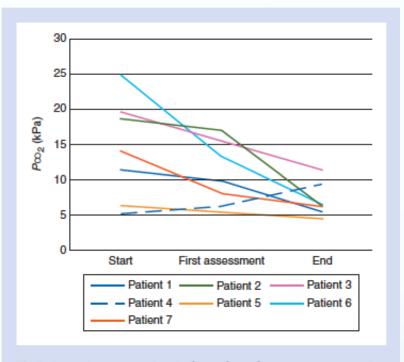


Fig 2 Pco $_2$  values per patient before, after a first assessment, and at the end of treatment with sevoflurane. The dashed line shows the patient who did not respond to sevoflurane therapy.

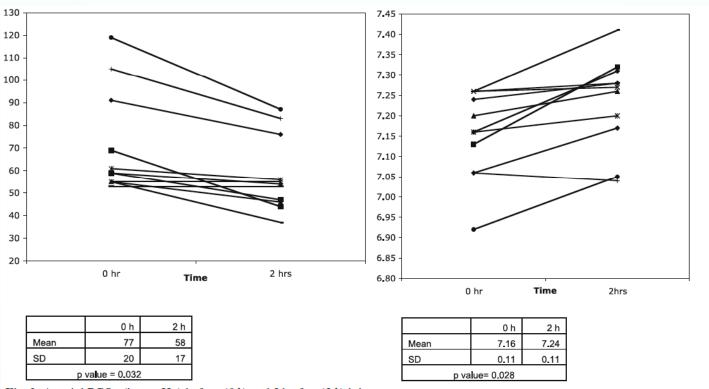


Fig. 2 Arterial PCO2 (in mmHg) before (0 h) and 2 h after (2 h) ini- Fig. 3 Arterial pH before (0 h) and 2 hours after (2 h) initiation of tiation of isoflurane

isoflurane

Shankar V, et al. Int Care Med 2006; 32:927-933.

	Inhaled Anesthetic $(n = 46)$	Conventional Ventilation (n = 1498)	P-value
Age, years (median, IQR)	4.5 (2,8)	7 (3,11)	0.03
Steroids (n, %)	44 (96)	1,365 (91)	0.29
Inhaled albuterol (n, %)	35 (78)	1,320 (88)	0.001
Inhaled ipratropium (n, %)	27 (59)	1,040 (69)	0.02
Magnesium (n, %)	24 (52)	713 (48)	0.75
Methylxanthines (n, %)	5 (11)	200 (13)	0.63
Terbutaline (n, %)	15 (33)	541 (36)	0.12
Any β-agonist (n, %)	36 (78)	1,381 (92)	0.002
Antibiotics (n, %)	46 (100)	956 (64)	<0.001
Paralytics (n, %)	40 (87)	666 (44)	<0.001
Heliox (n, %)	4 (9)	344 (23)	0.02

Char DS, et al. Pediatr Crit Care Med 2013; 14:343-350.

	Inhaled Anesthetic (n = 46)	Conventional Ventilation (n = 1498)	P-value
Days of ventilation (median, IQR)	6 (3,9)	2 (1,4)	<0.001
Hospital stay, days (median, IQR)	11 (5,16)	7 (3,11)	<0.001
Pneumothorax (n, %)	0	36 (2)	0.29
Pneumomediastinum	0	26 (2)	0.35
Aspiration pneumonia (n, %)	3 (6)	29 (2)	0.03
Cardiac arrest (n, %)	0	31 (2)	0.19
Death (n, %)	1 (2)	31 (2)	0.32
Hospital charges (median, IQR)	US\$91K (39K,166K)	US\$35K (19K,71K)	<0.001

Char DS, et al. Pediatr Crit Care Med 2013; 14:343-350.

## Summary

- Briefly reviewed epidemiology of childhood asthma exacerbations
- Initial therapy frequent high-dose beta-agonists, systemic corticosteroids
- Use "adjunct therapies" as needed in evidence based fashion

May there never develop in me the notion that my education is complete, but give me the strength and leisure and zeal continually to enlarge my knowledge.

Maimonides