Terapias Coadyuvantes para las Exacerbaciones del Asma

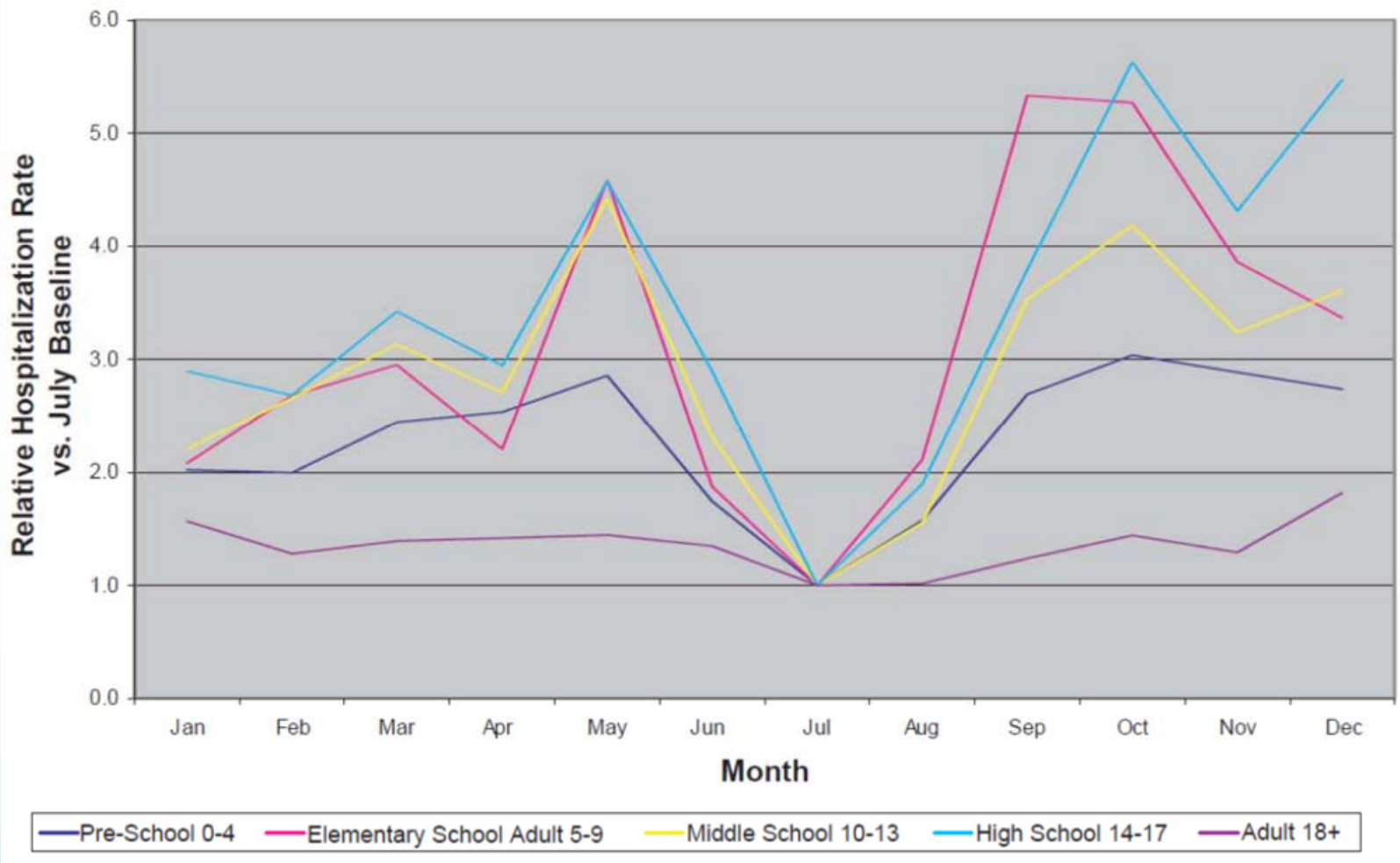
Mark A Brown, MD
Professor of Pediatrics
University of Arizona
brown6@email.arizona.edu

Objectives

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

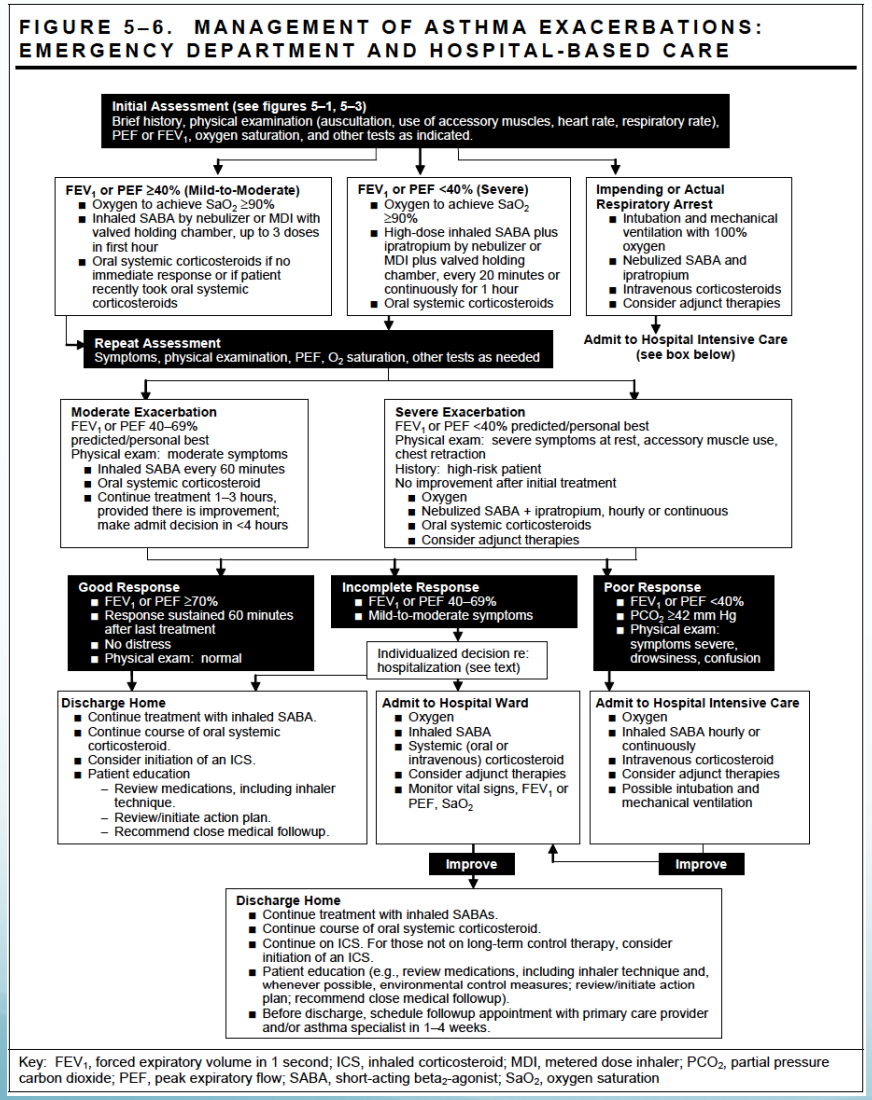
Definitions

- 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



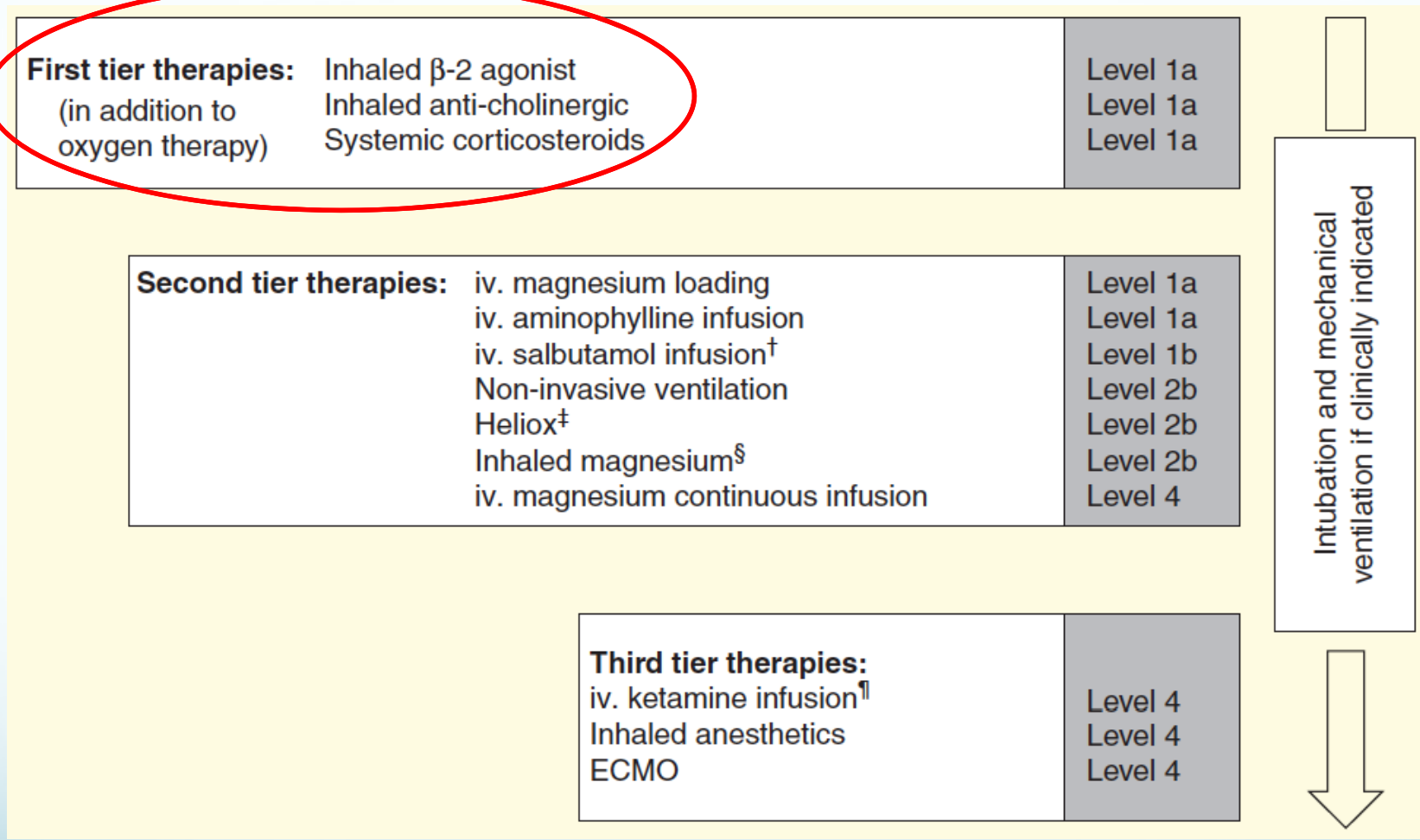
Blando, et al. Atmosphere 2012; 3: 200-212.

Initial Therapy



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

Therapy Escalation



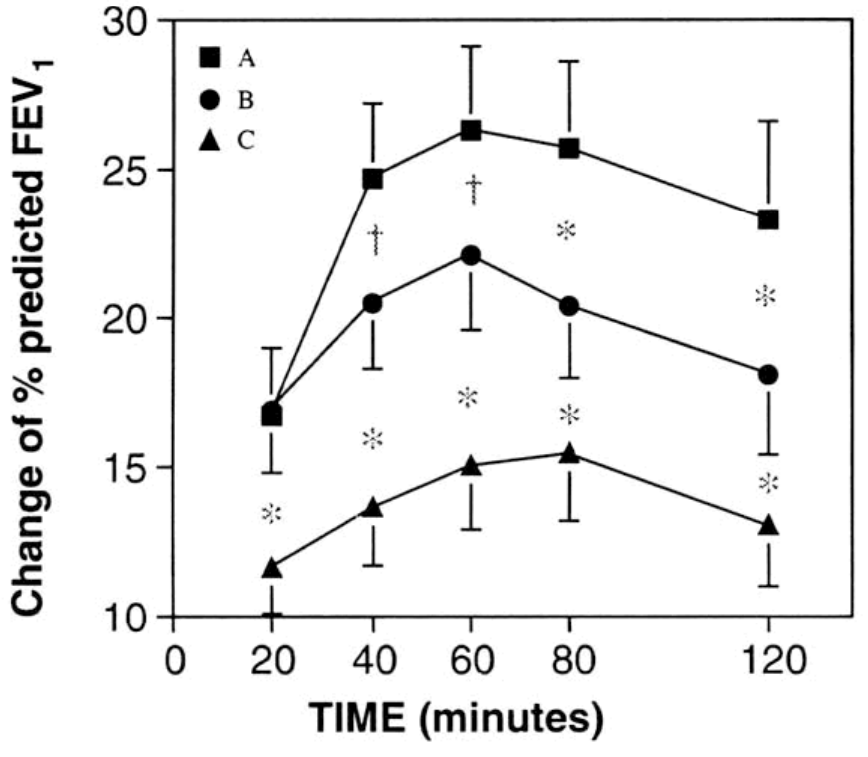
Wong, et al. Expert Rev Respir Med 2014; 8:423-441.

Bronchodilators

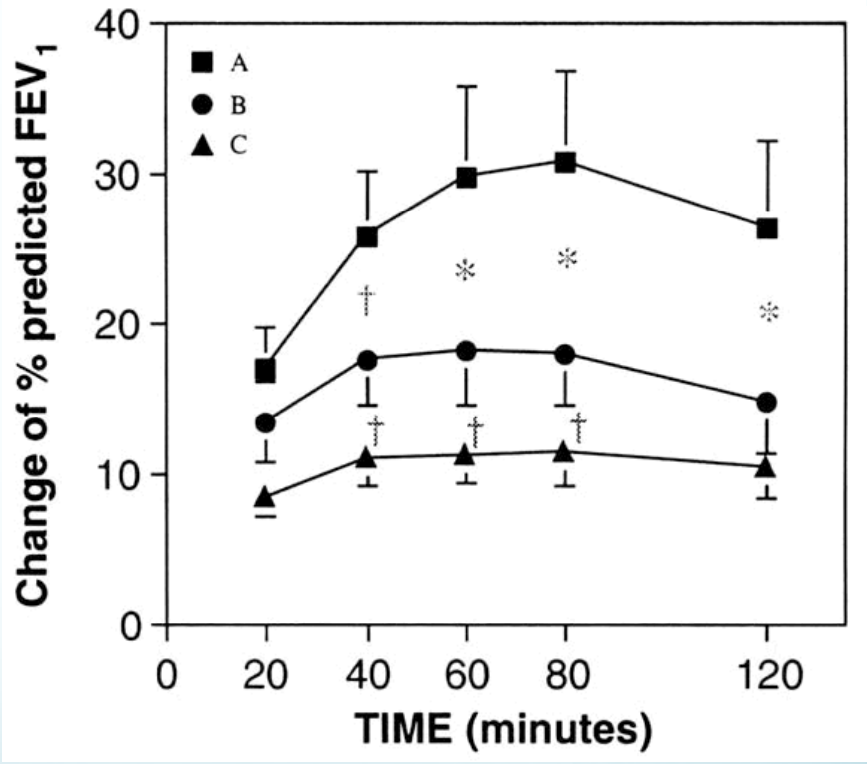
- High dose, selective β_2-agonists preferred
- Initially every 20 minutes (or continuously) for the first hour
  - Onset of action <5 minutes
  - Peak action 15-20 minutes
- Either nebulizer or MDI administration acceptable
- Anticholinergic should be added

Inhaled Anticholinergic - Ipratropium

FEV_1 30-50% predicted



FEV_1 <30% predicted



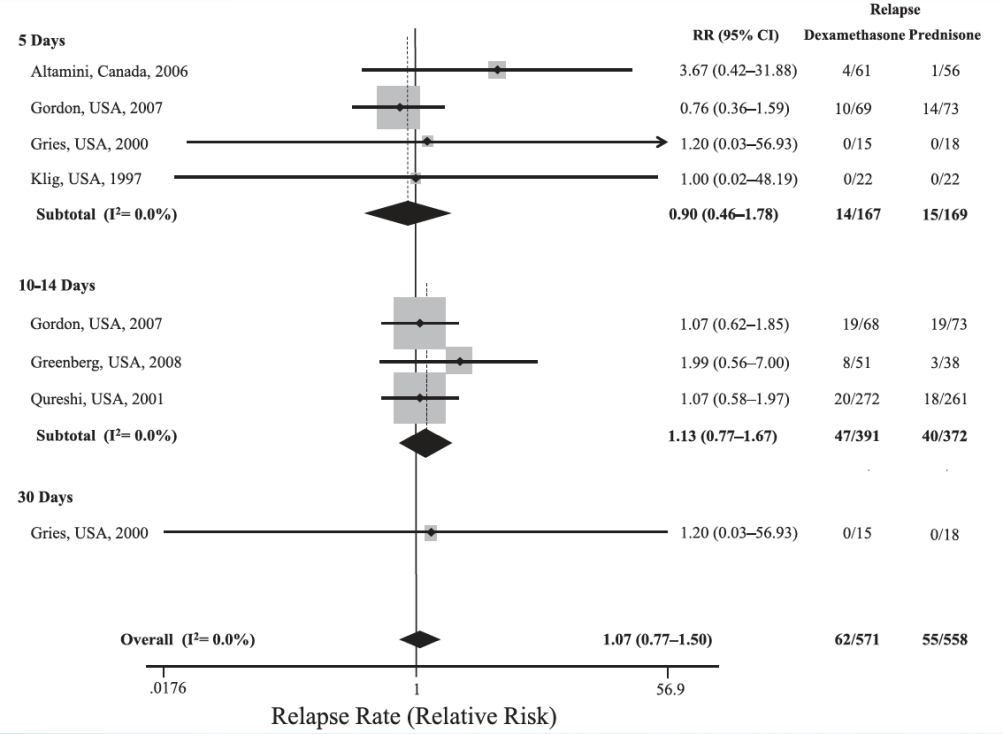
A = 3 doses (N=40)
B = 1 dose (N=39)
C = none (N=41)

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

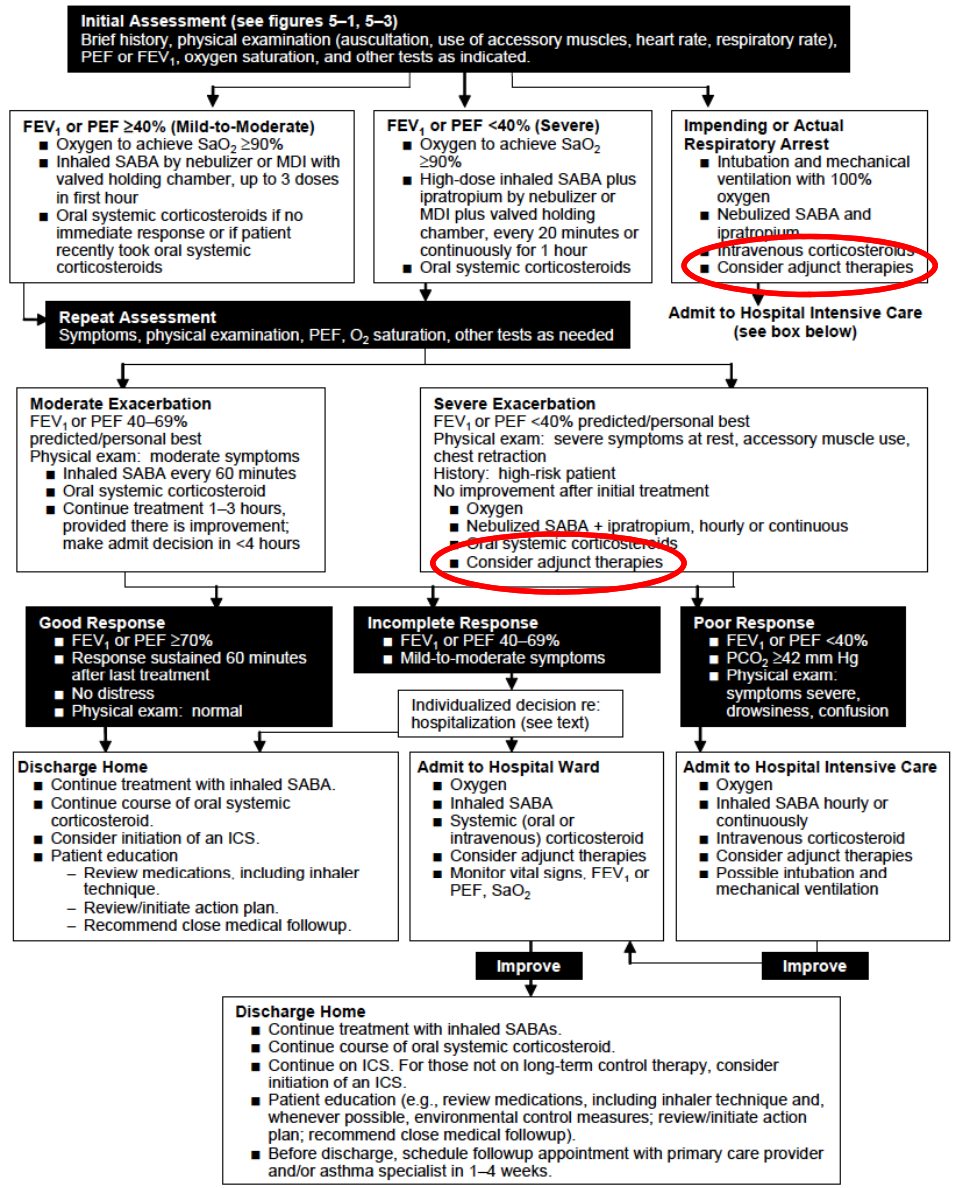
Prednisone vs Dexamethasone



- 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



Key: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; MDI, metered dose inhaler; PCO_2, partial pressure carbon dioxide; PEF, peak expiratory flow; SABA, short-acting beta$_2$-agonist; SaO_2, oxygen saturation

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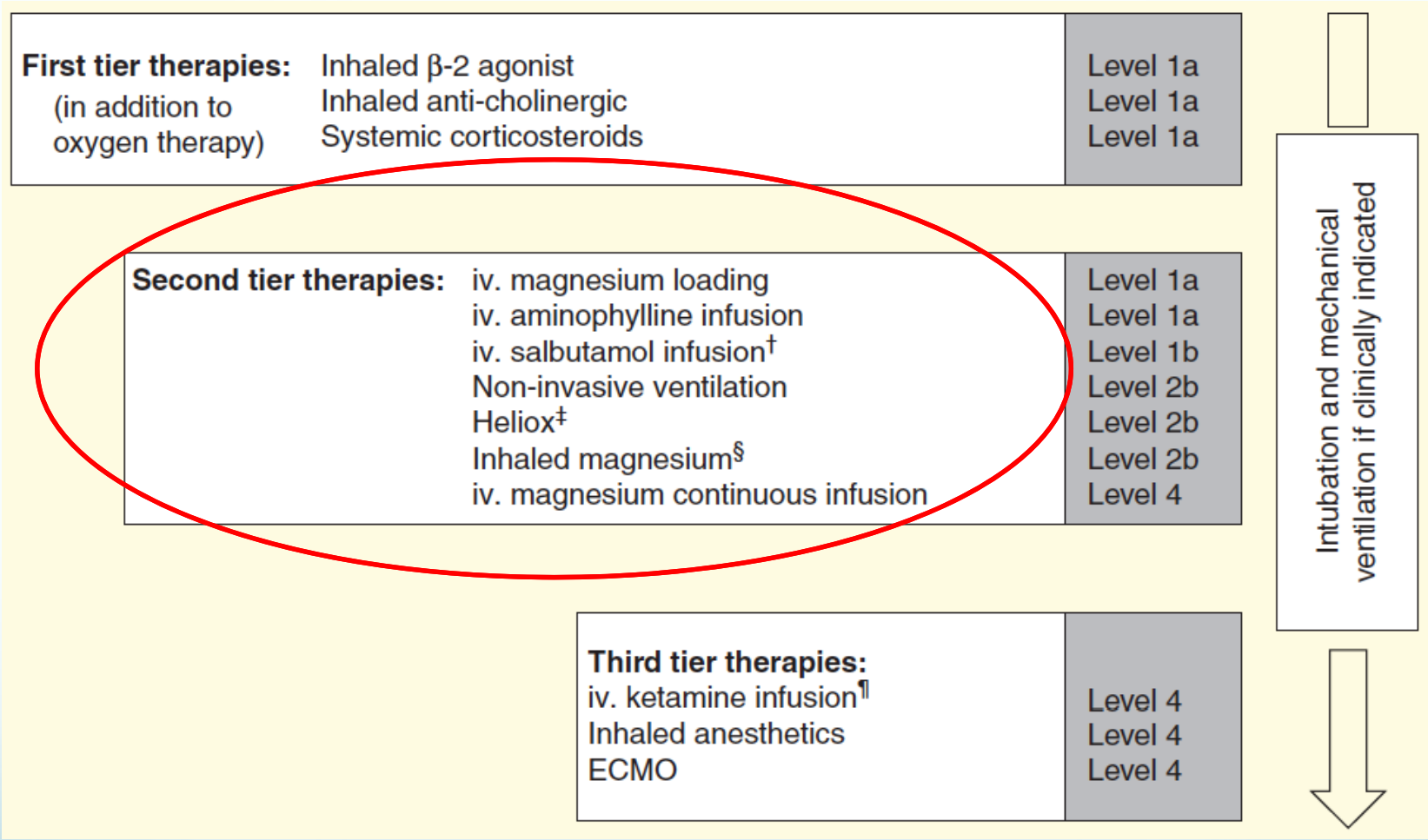
Therapy Escalation



Wong, et al. Expert Rev Respir Med 2014; 8:423-441.

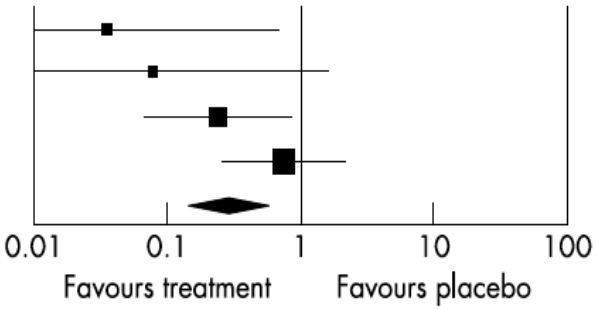
Magnesium

- 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**

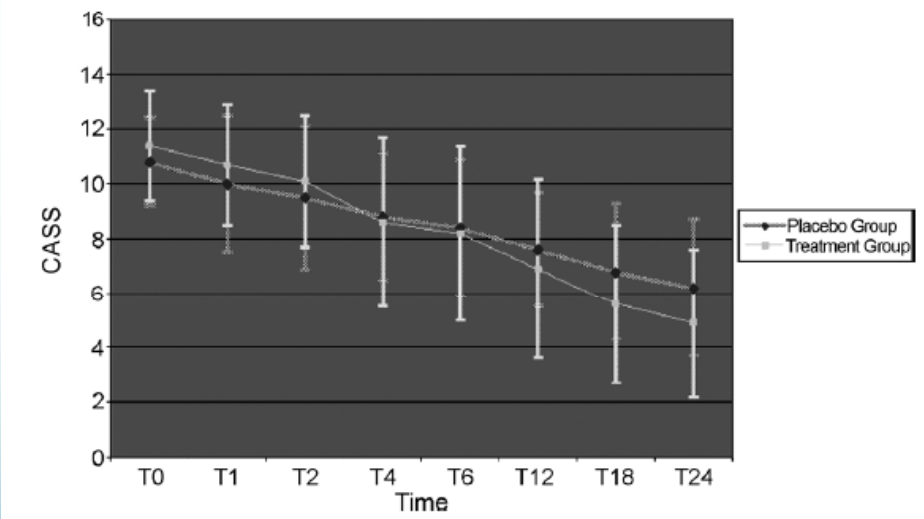


Cheuk, et al. Arch Dis Child 2005; 90:74-77.

- Roles for continuous infusion or inhaled magnesium unclear - investigational

Intravenous β-agonist

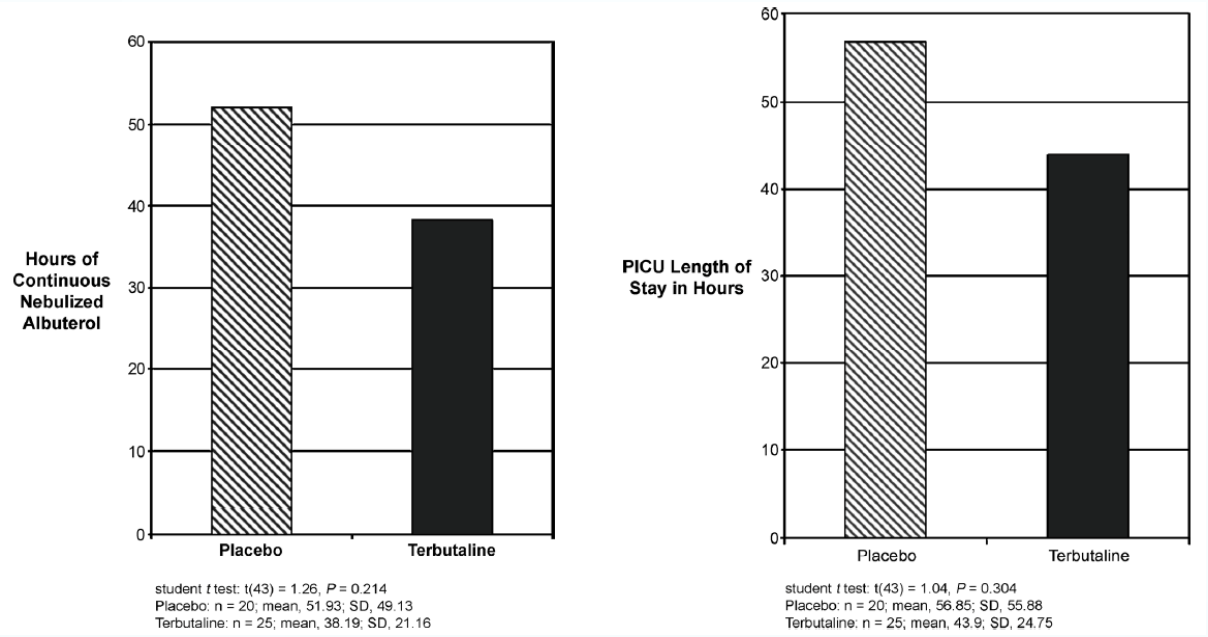
- Salbutamol frequently used world-wide
- Terbutaline used in US
- Evidence for efficacy of either is lacking.



- 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_1 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

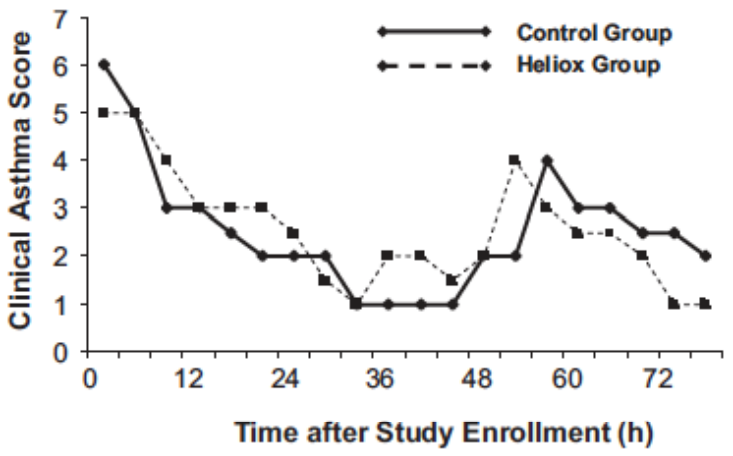


Table 3. Key study end points for heliox (n = 22) versus control (n = 20) study groups

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

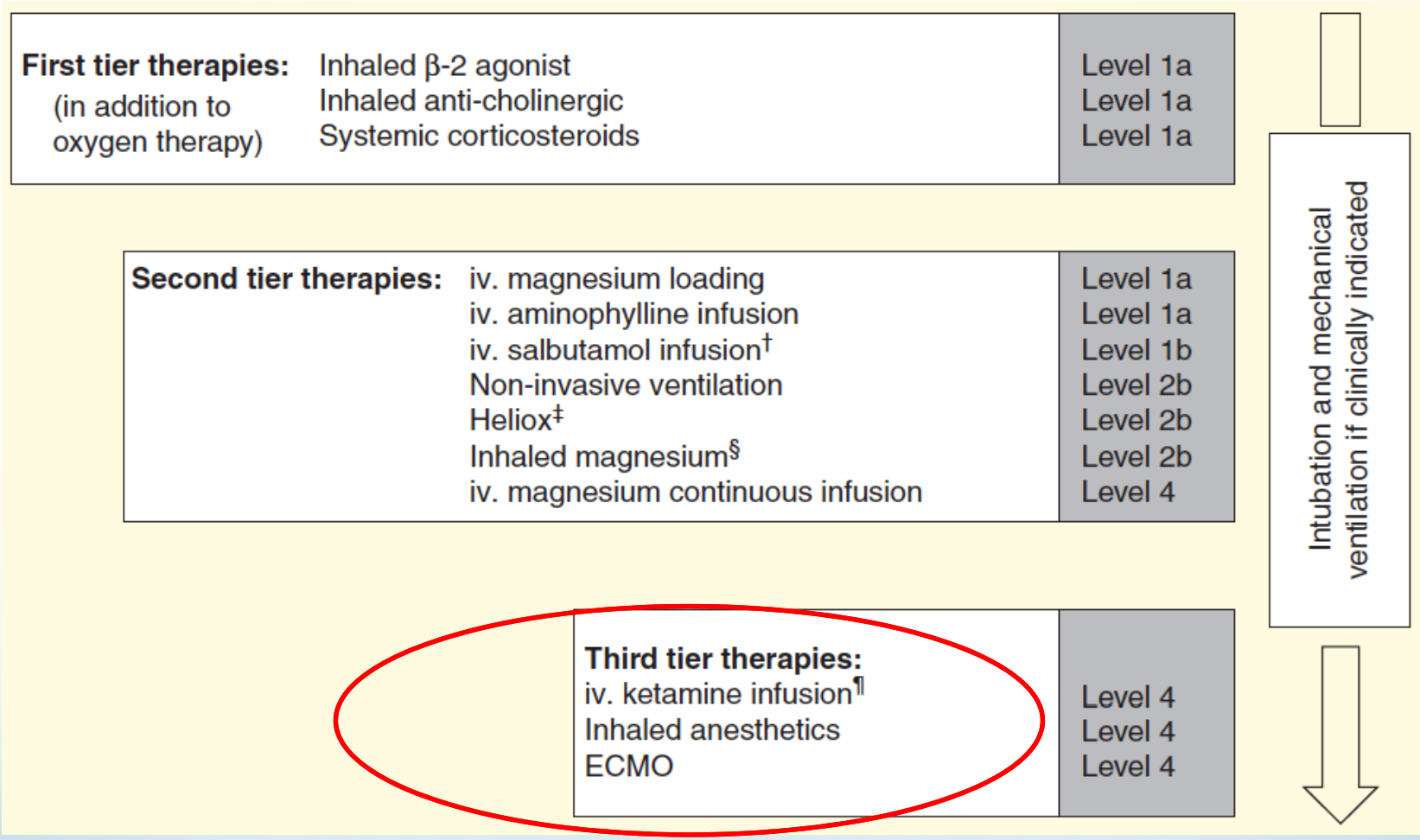
Table 4. PICU subgroup analysis of key study end points for heliox (n = 17) versus control (n = 17) study groups

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



Wong, et al. Expert Rev Respir Med 2014; 8:423-441.

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

Inhaled Anesthetics

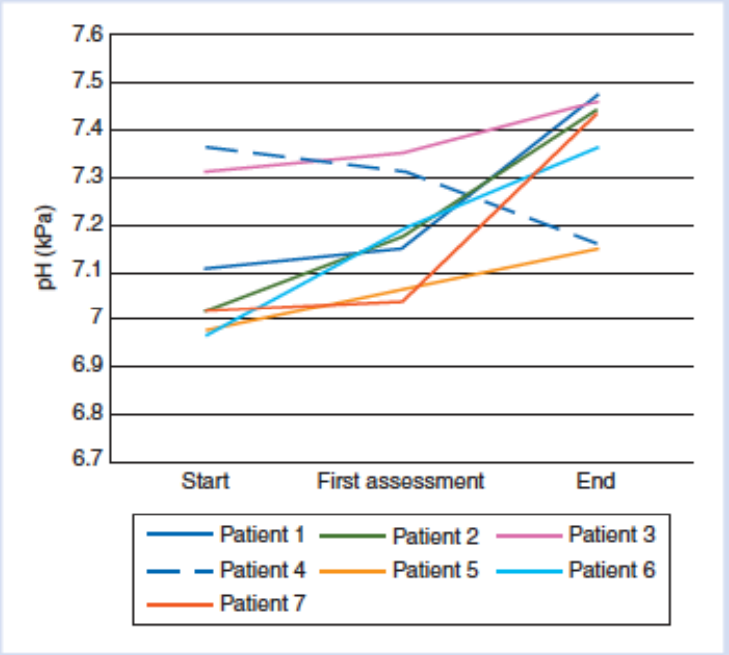


Fig 1 pH values per patient before, after a first assessment, and at the end of treatment with sevoflurane. The dashed line shows the patient who did not respond to sevoflurane therapy.

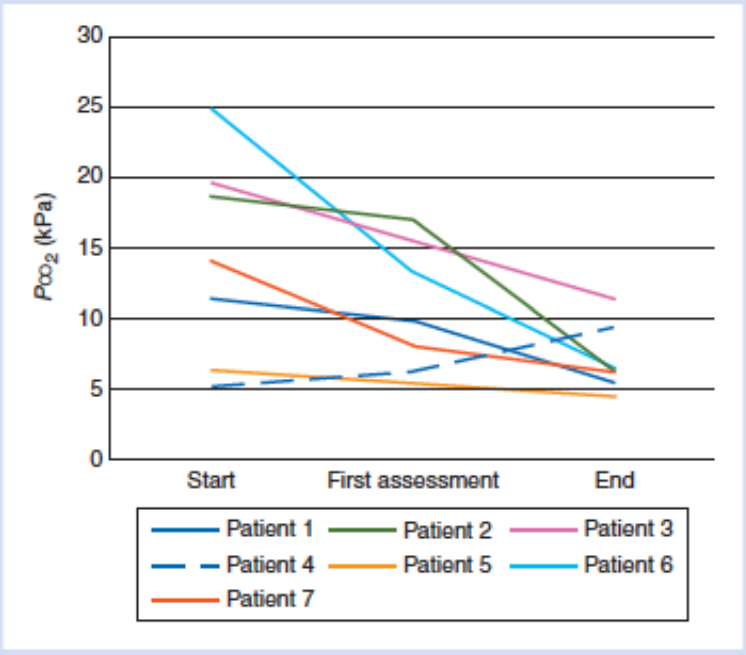
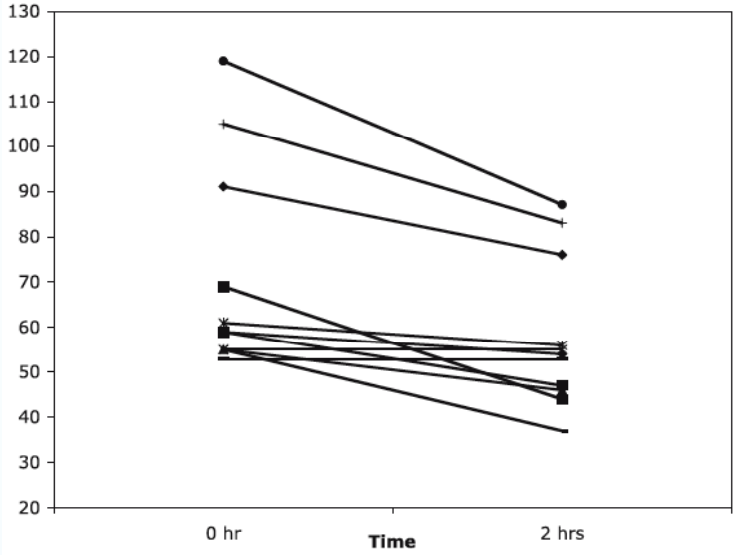


Fig 2 P_{CO_2} values per patient before, after a first assessment, and at the end of treatment with sevoflurane. The dashed line shows the patient who did not respond to sevoflurane therapy.

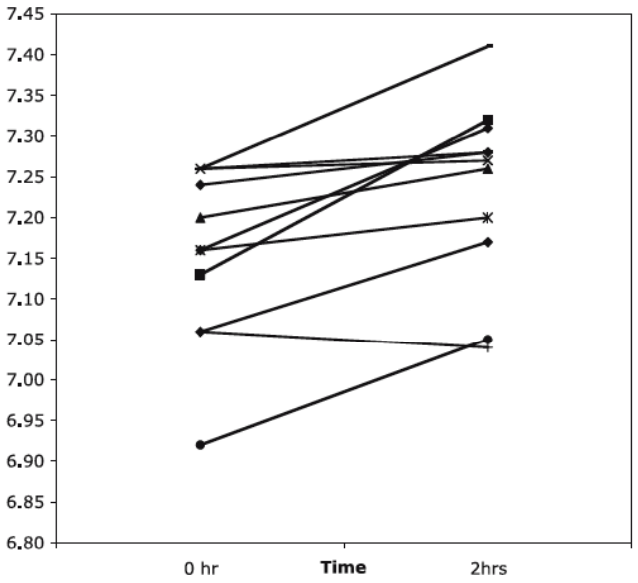
Schutte D, et al. Brit J Anaesth 2013; 111:967-970.

Inhaled Anesthetics



	0 h	2 h
Mean	77	58
SD	20	17
p value = 0.032		

Fig. 2 Arterial PCO_2 (in mmHg) before (*0 h*) and 2 h after (*2 h*) initiation of isoflurane



	0 h	2 h
Mean	7.16	7.24
SD	0.11	0.11
p value= 0.028		

Fig. 3 Arterial pH before (*0 h*) and 2 hours after (*2 h*) initiation of isoflurane

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

Inhaled Anesthetics

	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 Anesthetics

	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