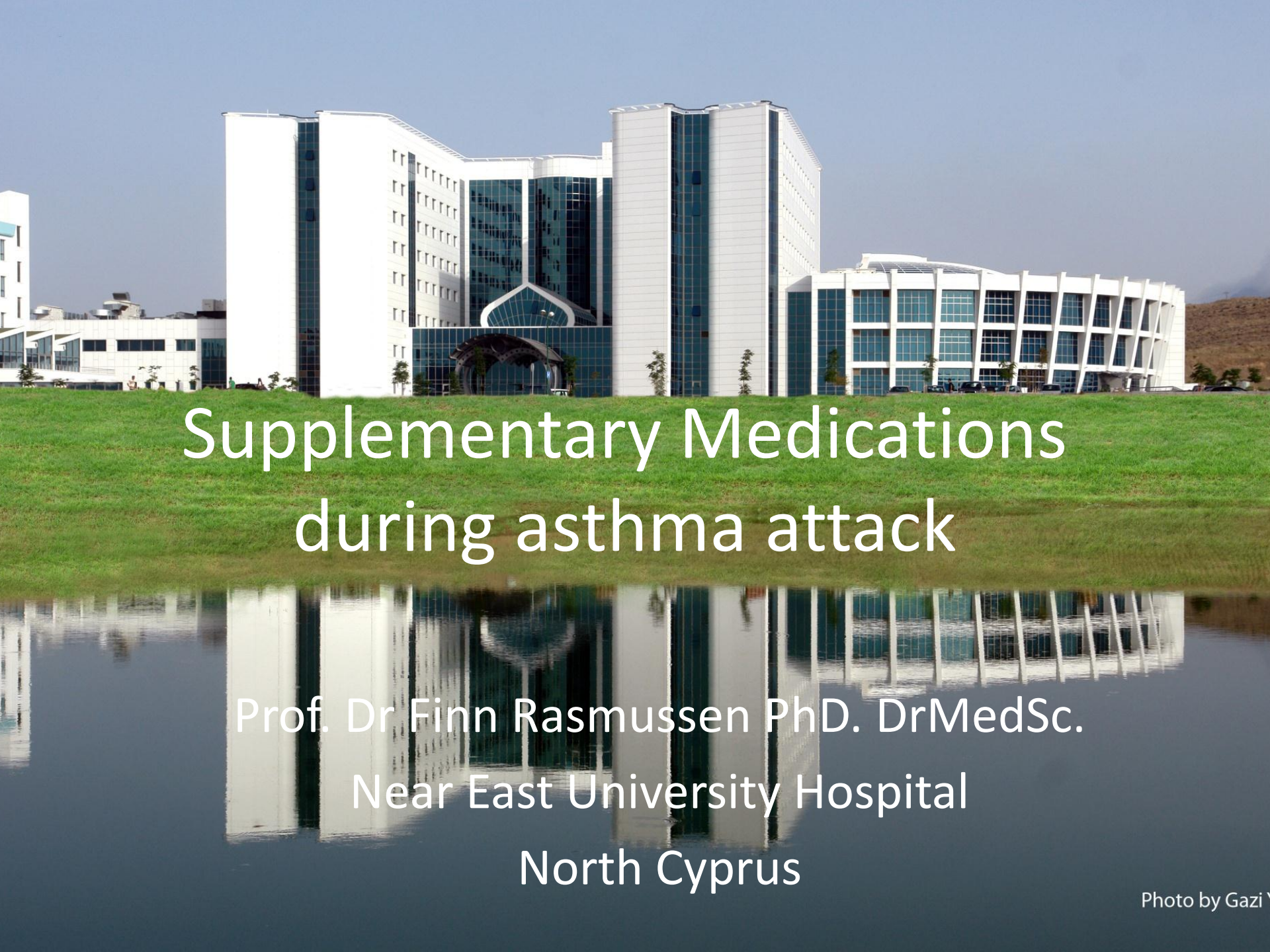


Supplementary Medications during asthma attack

Prof. Dr Finn Rasmussen PhD. DrMedSc.
Near East University Hospital
North Cyprus

Photo by Gazi

Conflicts of Interest

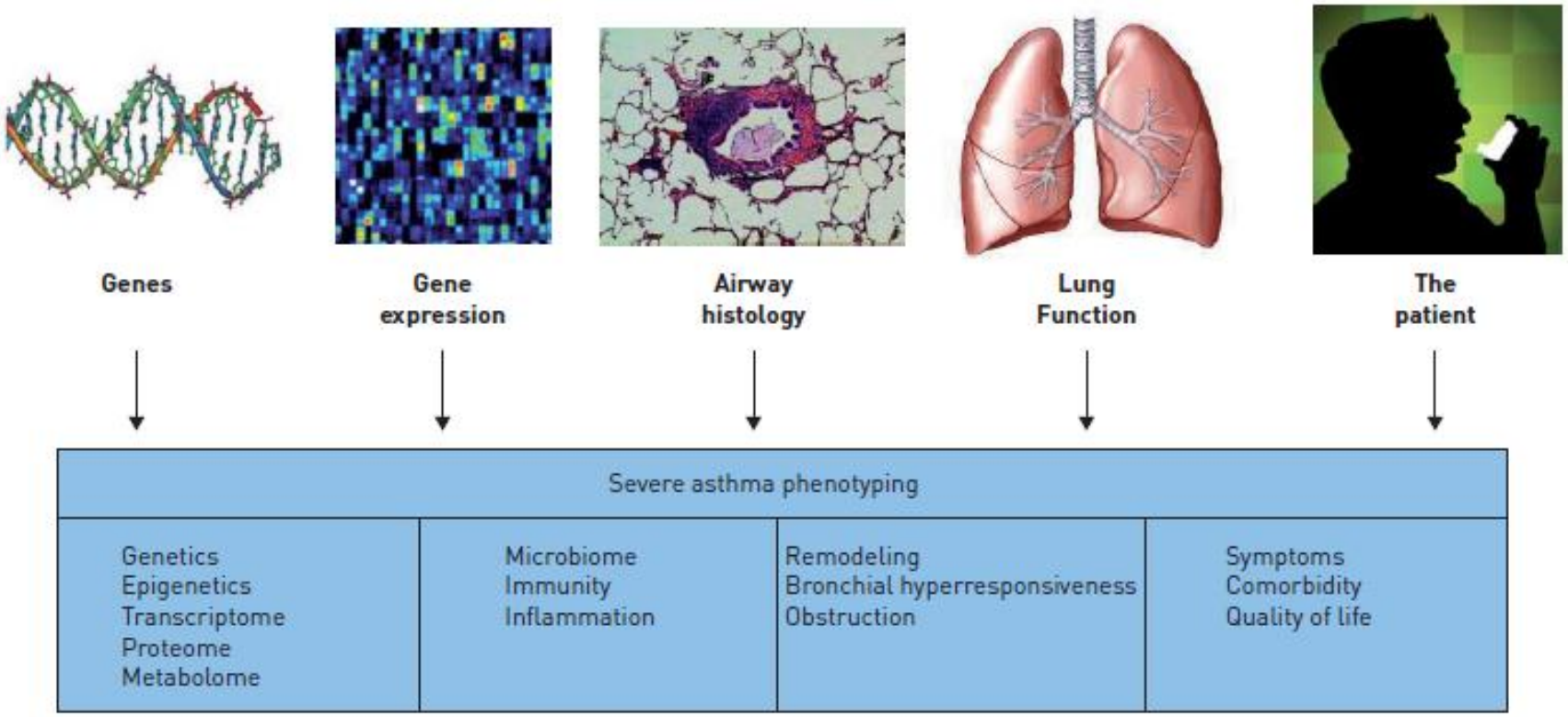
- None

Definition of Asthma

Airway narrowing that is reversible (± completely)

Heterogeneous group with episodic symptoms:

Shortness of breath, Wheezing, Cough



RE 1 Integration of factors, beginning with genetics, which may contribute to the ultimate phenotype of the severe asthma patient.

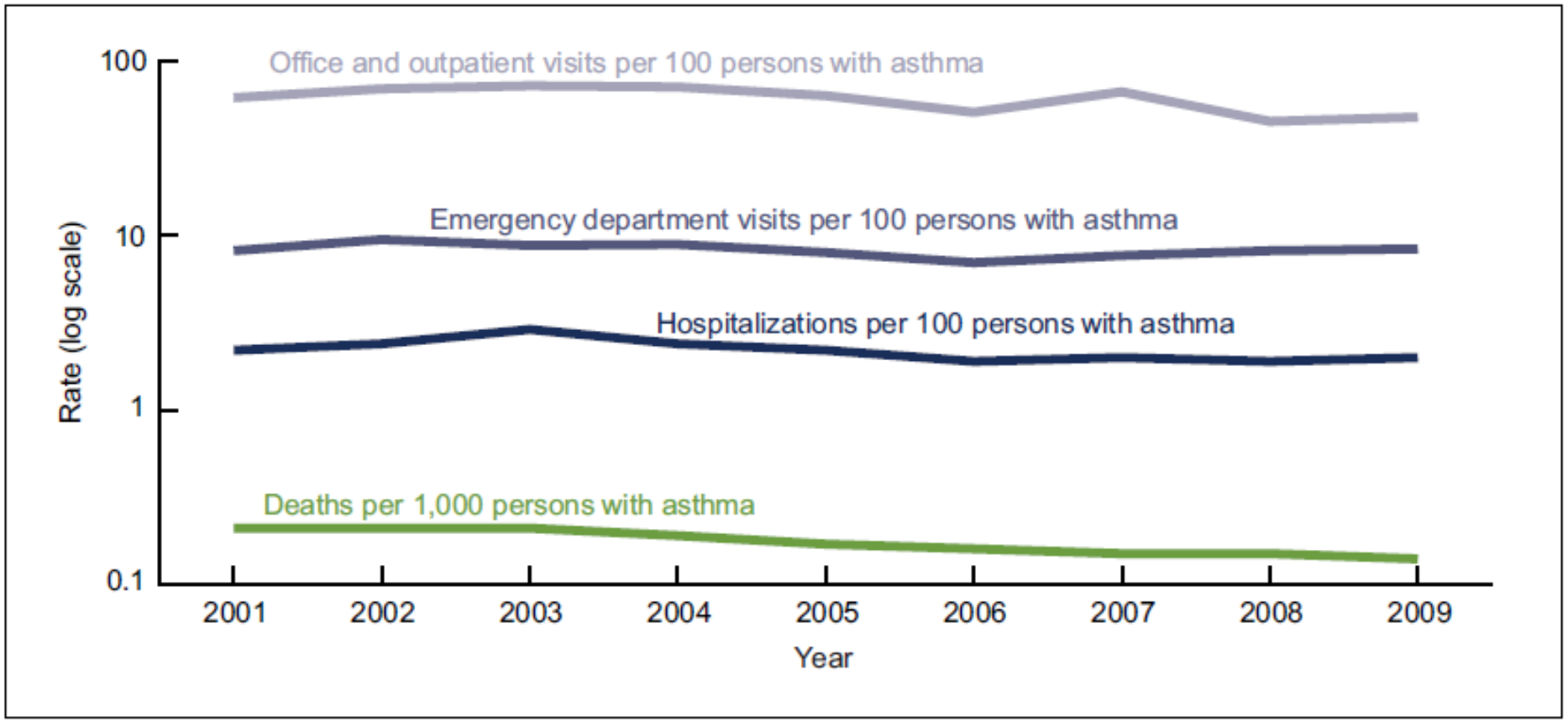
Asthma attack rates : children 54.6 and adults 39.4 per 1,000, respectively

DOI: 10.1183/09031936.00202013

Big problem

but not getting worse

Figure 3. Asthma health care encounters per 100 persons with asthma, and asthma deaths per 1,000 persons with asthma: United States, 2001–2009



NOTE: Access data table for Figure 3 at: http://www.cdc.gov/nchs/data/databriefs/db94_tables.pdf#3.

SOURCES: CDC/NCHS, National Ambulatory Medical Care Survey, National Hospital Ambulatory Medical Care Survey, National Hospital Discharge Survey, National Vital Statistics System, and National Health Interview Survey.

Supplementary Medications during asthma attack

Emergency room visits

A emergency room visit with asthma exacerbations:

-Generally a failure of the current treatment!!

-Occur when a person's asthma is not under control

allergic, infection, compliance, irritants

-New asthma

Gina 2009; Camargo CA Jr, on behalf of the MARC Investigators. Management of acute asthma in US emergency departments: the Multicenter Asthma Research Collaboration *American Journal of Respiratory and Critical Care Medicine* 1998;157:A623.

Supplementary Medications during asthma attack
ED Management: Goals

1. Correct significant hypoxemia
2. Rapidly reverse airflow obstruction
3. Decrease likelihood of recurrence
4. Avoid hospitalization

NAEPP, 1997; GINA 2011

Supplementary Medications during asthma attack

Normal treatment in ED

Mild Exacerbations:

Oxygen to achieve O2 saturation ≥ 92% (95% in children)

Inhaled rapid-acting beta2-agonist and *anti-cholinergic agents*

Moderate to severe Exacerbations: (if no immediate response)

Above +

Glucocorticosteroids (inhaled and oral):

-recently took oral glucocorticosteroid,

-episode is severe.

Clinic Rev Allerg Immunol DOI 10.1007/s12016-014-8408-0;Gina 2011

Supplementary medications during asthma attack

First-Line Therapy

Protocols of Ipratropium Plus Albuterol in the Emergency Department

Randomized, double-blind, controlled trials:
If High doses of Ipratropium and albuterol are combined (multiple-dose protocol) in the emergency treatment of acute severe Asthma:

<u>Adults:</u>
Mean FEV1 increase: 0.5L, (95%CI: 0.28 to 0.72 L)
Lower rates of hospital admissions
(RR:0.51, 95%CI:[0.31,0.83] NNT=5)

<u>Children and adolescents:</u>
Lower rates of hospital admissions (30% reduction in hospital admission rate)
(RR:0.72, 95%CI: [0.53;0.99], NNT: 11)
<u>Use spacers !!</u>

Thorax 2005;**60**:740–746. doi: 10.1136/thx.2005.040444

Am J Respir Crit Care Med Vol 161. pp 1862–1868, 2000
J. Allergy Clin. Immunol. 81:16–20.; J. Allergy Clin. Immunol. 82:1012–1018.;
J. Pediatr. 1995;126:639–645. *Ann. Emerg. Med. 1997 29:205–211.*

Supplementary “medications” during asthma attack

- doctors care actions matters

Care of patients discharged with an acute asthma attack should generally include:

1) A minimum 3- to 7-day course of oral corticosteroids
2) Initial or continued use of controller therapy
3) Review of inhaler technique and use of peak flow meter
4) Identification of potential triggers of exacerbations
5) Provision of a written action plan for prevention of future exacerbations
6) Encouragement to contact a physician within one week after discharge for a follow-up appointment

Bateman ED, Hurd SS, Barnes PJ, *et al. Global strategy for asthma management* and prevention: GINA executive summary. *Eur Respir J 2008;**31:143-78.*** http://dx.doi.org/10.1183/09031936.00138707

Supplementary Medications during asthma attack - candidates?

- Magnesium
- Heliox
- Leukotriene antagonists
- Methylxanthines
  - Aminophylline (intravenous)
- $Beta_2$- agonist (intravenous)
- Ketamine

Supplementary Medications during asthma attack - candidates?

- Magnesium
- Heliox
- Leukotriene antagonists
- Methylxanthines
  - Aminophylline (intravenous)
- Iv $Beta_2$- agonist
- ketamine

Supplementary Medications during asthma attack

Magnesium

Why it could work:

Powerful airway smooth muscle relaxant.

- inhibition of the interaction between calcium and myosin results in muscle cell relaxation
- In cholinergic motor nerve terminals, magnesium depresses muscle fiber excitability by inhibiting acetylcholine release

IV or nebulization

Intravenous magnesium is a weak bronchodilator in stable asthmatic patients

Magnesium administered directly to the airways by nebulization prior to challenge testing may cause a dose-dependent reduction in bronchial hyperresponsiveness.

Curr Opin Allergy Clin Immunol 7:107–110. 2007

Supplementary Medications during asthma attack
Magnesium
Do we need to ask ?

British guideline on the management of asthma (January 2012) : Single dose of intravenous Magnesium sulfate has been shown to be safe and effective in adults.

Consider giving a single dose of IV magnesium sulphate for patients with:

- **Acute severe asthma who have not had a good initial response to inhaled bronchodilator therapy**
- **Life threatening or near fatal asthma.**

The guidelines for children are more equivocal, suggesting that intravenous magnesium sulfate is safe but its place in management is not yet established

British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN). British guideline on the management of asthma. A national clinical guideline. (SIGN publication no. 101).

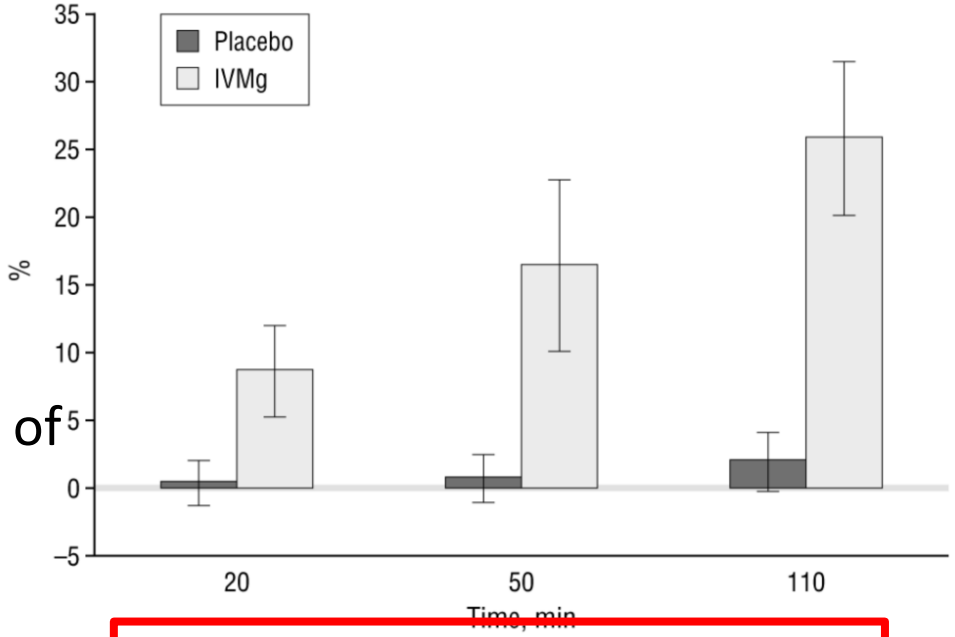
Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma children.

Double-blind placebo controlled Trial
2 centers.

30 patients, aged 6 to 18

Treatment: Magnesium sulfate infusion of 40 mg/kg or saline solution (max 2g)

Inclusion: after 3 times nebulized Bronchodilating (B_2) and/or anti-cholinergics treatments and still a PEF<70%



All 14 of the placebo-treated patients required admission to the hospital, whereas 8 (50%) of 16 patients who received IV Mg were discharged to their homes (*P* =0.002).

Arch Pediatr Adolesc Med 2000; 154:979–983

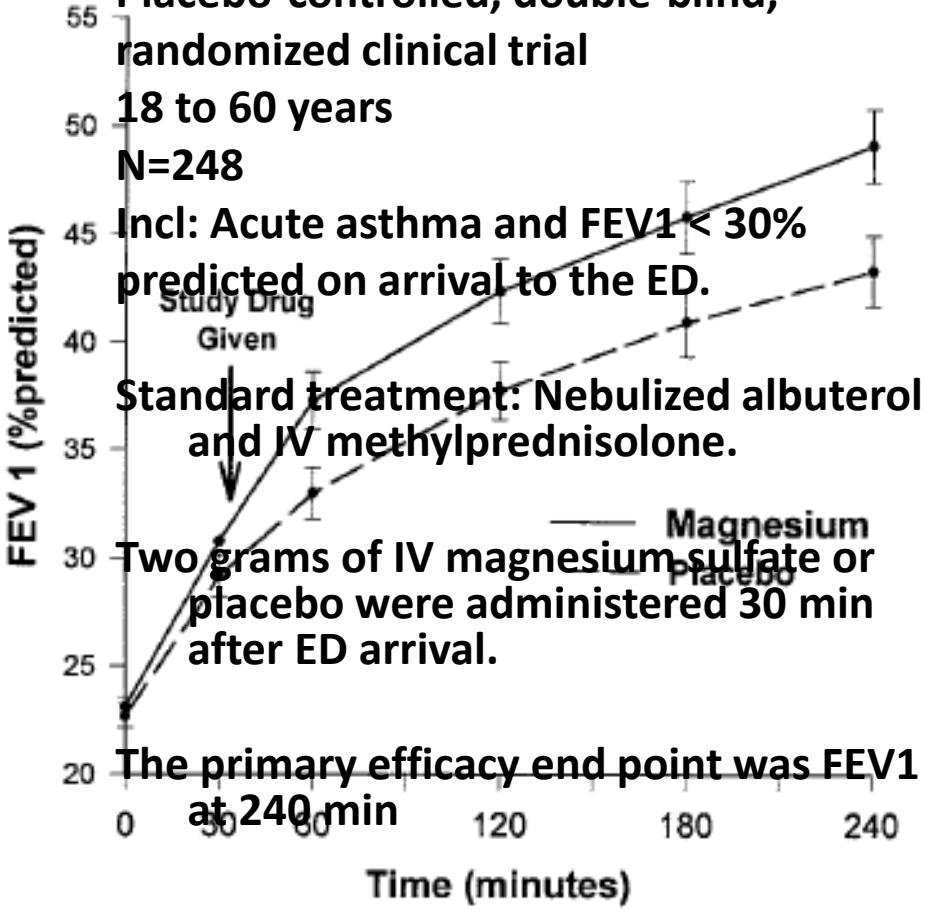
IV Magnesium Sulfate in the Treatment of Acute Severe Asthma
adults

Placebo-controlled, double-blind, randomized clinical trial
18 to 60 years
N=248
Incl: Acute asthma and FEV1 < 30% predicted on arrival to the ED.

Standard treatment: Nebulized albuterol and IV methylprednisolone.

Two grams of IV magnesium sulfate or placebo were administered 30 min after ED arrival.

The primary efficacy end point was FEV1 at 240 min



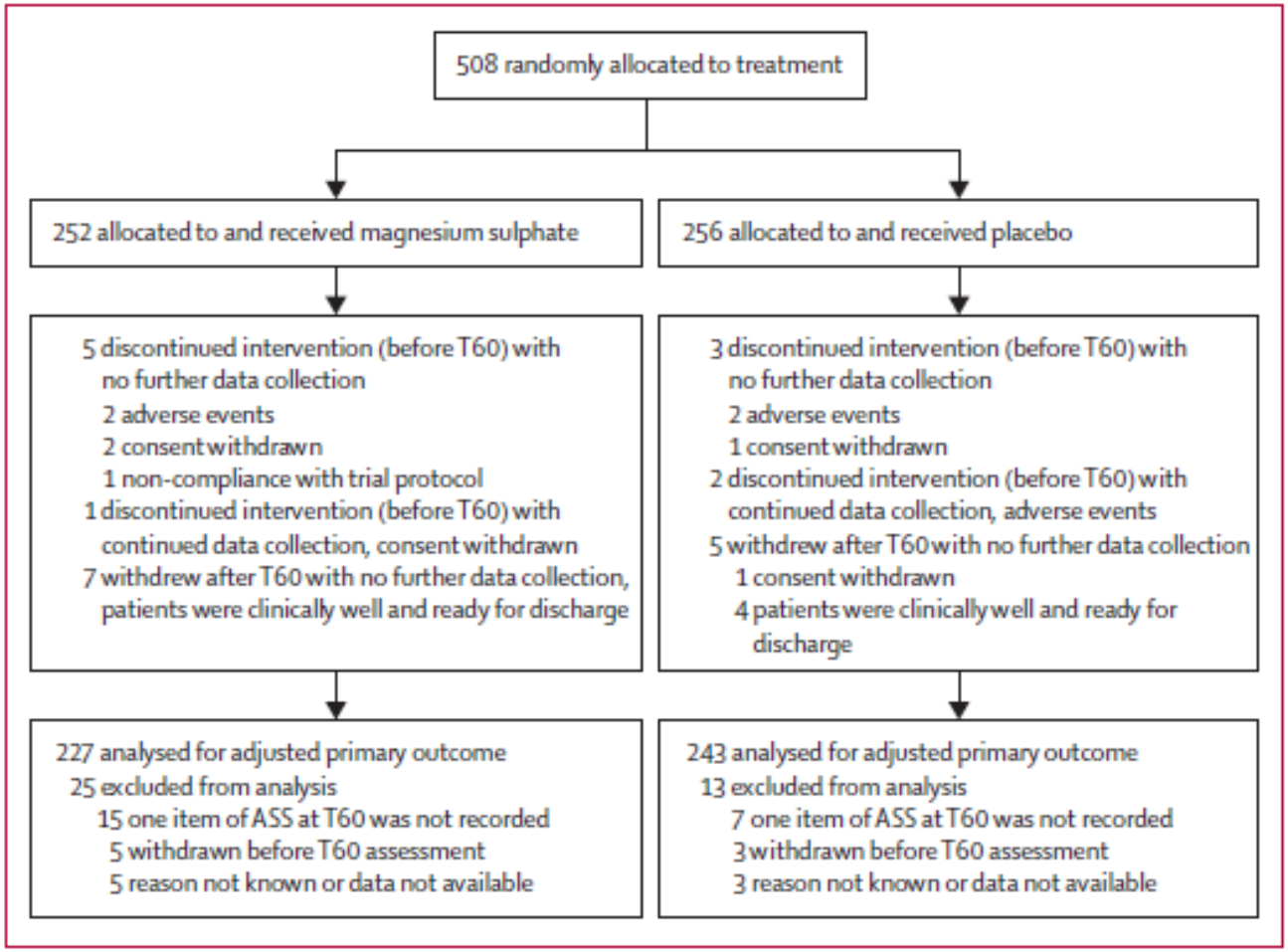
Receiving Mg mean FEV1 of 48.2% predicted, compared to 43.5% predicted in the placebo-treated group

(mean diff: 4.7% ; 95%CI[0.29;9.3]; p= 0.045).

Overall, the use of magnesium sulfate did not improve hospital admission rates.

CHEST 2002; 122:489–497

Inhaled Magnesium sulphate in acute severe asthma in children (MAGNETIC)



Randomised Placebo controlled, multi-centre, parallel trial
aged 2–16 years

The primary outcome measure was the Yung Asthma Severity Score (ASS) at 60 min

Standard therapy: Nebulised salbutamol and ipratropium bromide on three occasions at 20-min intervals.

Nebulized: 2,5 mL of isotonic MgSO4 (250 mmol/L; 151 mg per dose; MgSO4 group) 2·5 mL of isotonic saline (placebo group)

www.thelancet.com/respiratory **Vol 1 June 2013**

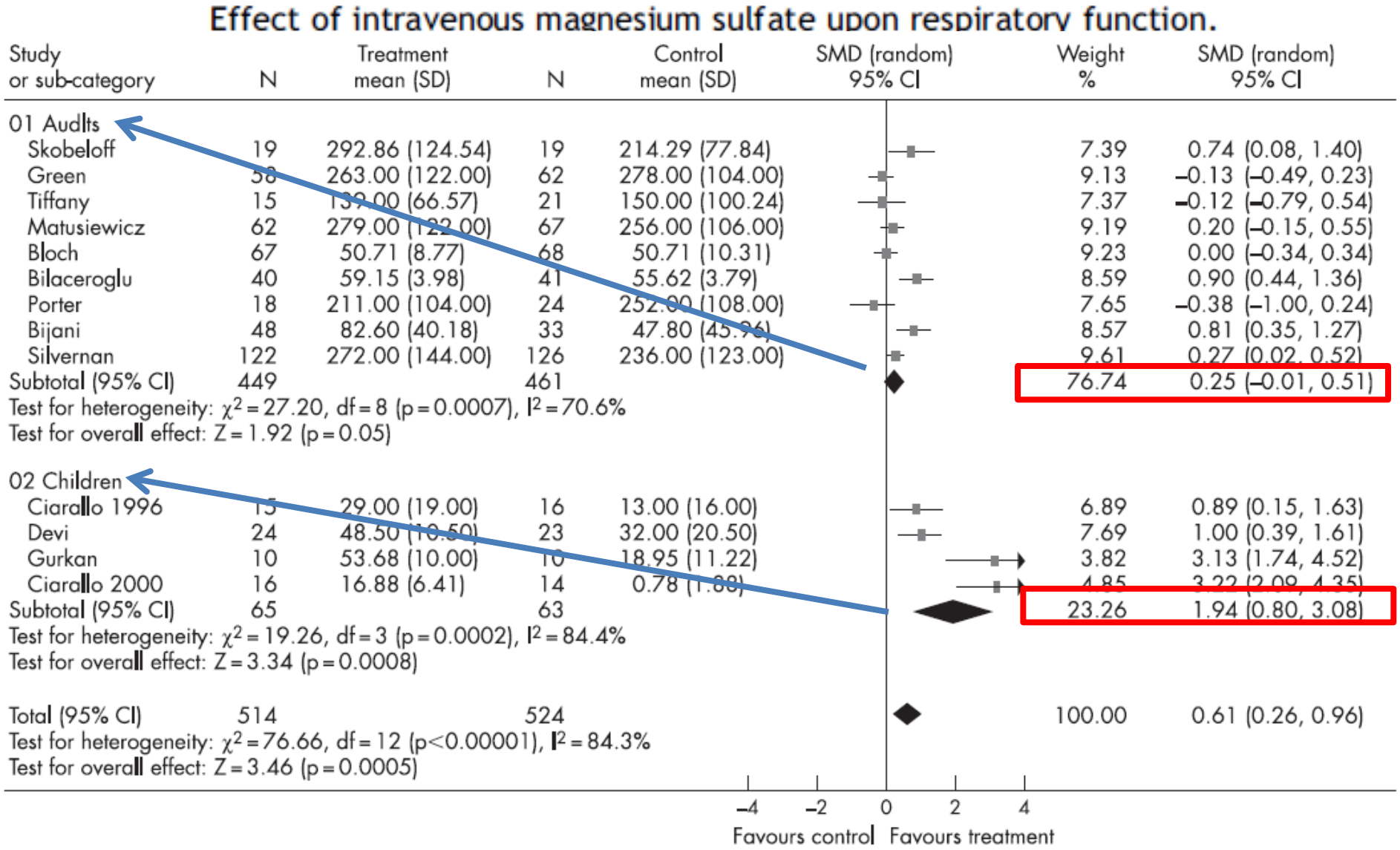
	$MgSO_4$ (n=228)	Placebo (n=244)	Difference in mean (95% CI); p value	Adjusted difference in mean (95% CI); p value*
Primary outcome				
ASS at 1 h	..	..	−0·24 (−0·49 to −0·02); p=0·006*	−0·25 (−0·48 to −0·02; p=0·034)
Number of patients	228	244	..	..
Mean (SD), range	4·72 (1·37), 2 to 9	4·95 (1·40), 2 to 9		
Secondary outcomes				
Step-down of treatment at 1 h	..	..	0	
Number of patients				
n/N (%)	82/248 (33%)	76/253 (30%)		
Number of additional salbutamol doses	247	253	−1	
Number of patients median (IQR)	8 (4 to 14)	9 (4 to 17)	..	..
Length of stay in hospital	..	..	−1·8 (−4·8 to 0·7); p=0·166	..
Number of patients	251	254	..	..
Median hours (IQR)	26·3 (17·4 to 44·8)	27·1 (19·2 to 47·6)	..	..
Proportion requiring intravenous bronchodilator treatment	..	..	−0·02 (−0·07 to 0·03); p=0·527	..
n/N (%)	24/249 (10%)	30/255 (12%)	..	..
Proportion requiring intubation or admission to a paediatric intensive care unit or high-dependency care†	..	..	0·03 (−0·02 to 0·07); p=0·283	..
n/N (%)	22/251 (9%)	15/254 (6%)	..	..

ASS=Yung asthma severity score. *When adjusted for baseline severity score. †35 children were admitted to paediatric intensive care for escalation of treatment and further observation due to the severity of their asthma and lack of response to initial treatment; there was only one child (in the placebo group) who required intubation.

Table 2: **Outcomes**

NB!!
The trial regarded a change in ASS of 0,5 to be the minimum worthwhile clinically important difference to be detected.

Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis



Same trend for hospital admission rates

Emerg Med J 2007;**24**:823–830. doi: 10.1136/emj.2007.052050

Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial): a double-blind, randomised controlled trial

Aged ≥16 years

Standard treatment of B_2 and anti-Cholinergics and prednisolone

1. IV MgSO4 (2 g in 20 min)

2. Nebulised MgSO4 (three 500 mg doses in 1 h)

3. Placebo

Primary outcome:

- **The proportion of patients admitted to hospital within 7 days**
- **Breathlessness measured on a 100 mm visual analogue scale (VAS) in the 2 h after initiation of treatment**

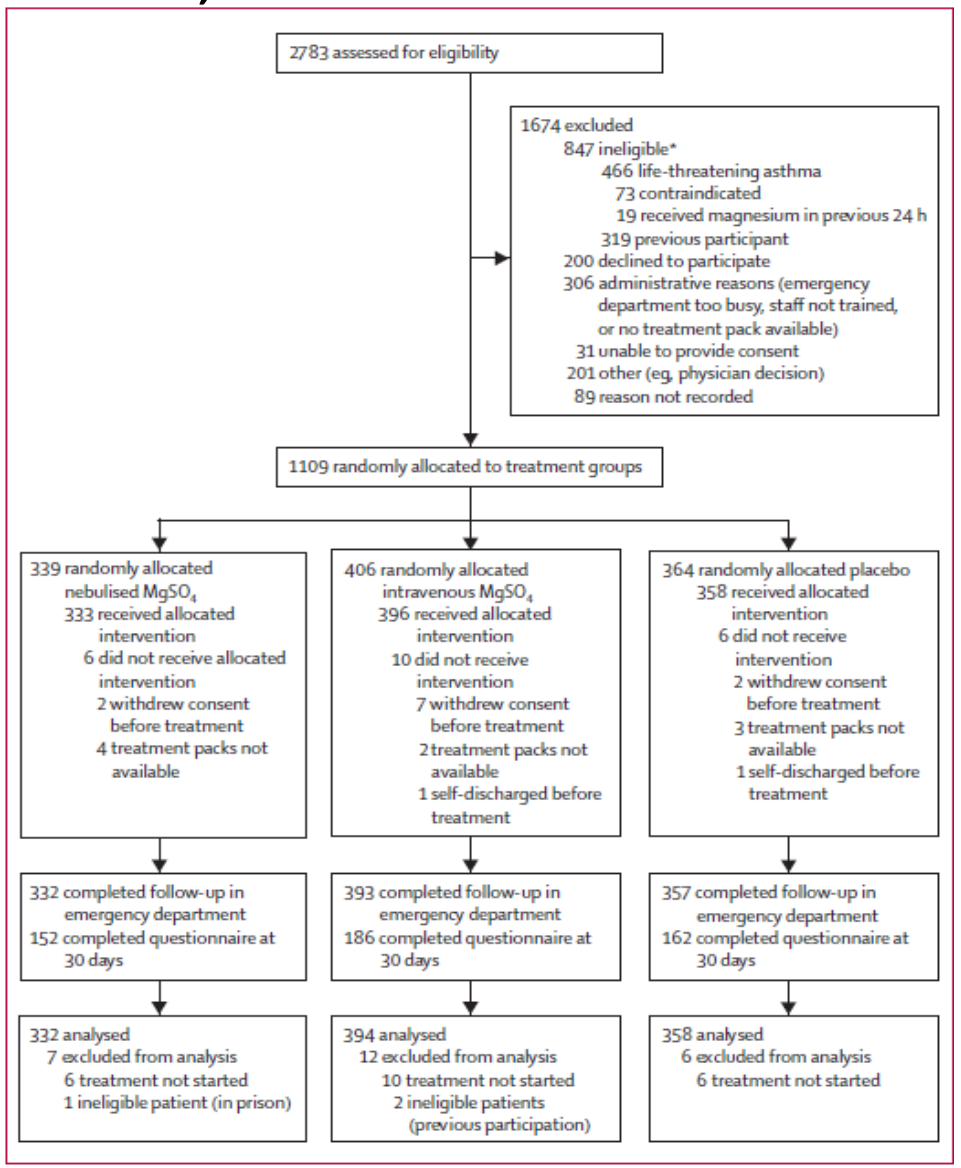


Figure 1: **Study profile**

*Patients could meet ≥1 exclusion criteria.

Change in VAS at 1 h			
Patients assessed	314 (95%)	372 (94%)	344 (96%)
Mean change, mm	−18·4 (22·8)	−24·2 (24·4)	−21·5 (24·7)
Change in VAS at 2 h			
Patients assessed	296 (89%)	357 (91%)	323 (90%)
Mean change, mm	−28·2 (27·4)	−34·3 (27·7)	−31·3 (29·4)

The findings suggest nebulised MgSO4 has no role in the management of severe acute asthma in adults and at best suggest only a limited role for in this setting of intravenous MgSO4

Why different:

Meta-analysis can be subject to publication bias if positive trials are preferentially submitted and accepted for publication.

	Nebulised $MgSO_4$ (n=332)	Intravenous $MgSO_4$ (n=384)	Placebo (n=358)	Overall (n=1084)
Admitted	254 (77%)	279 (71%)	278 (78%)	811 (75%)
Discharged	77 (23%)	114 (29%)	80 (22%)	271 (25%)
Died	0	0	0	0
Unknown	1 (<1%)	1 (<1%)	0	2 (<1%)
Subsequent hospital admission within 7 days	15 (5%)	10 (3%)	7 (2%)	32 (3%)
Subsequent hospital admission after discharge at initial attendance	6 (2%)	5 (1%)	3 (1%)	14 (1%)
Admitted to hospital at any time within 7 days	261 (79%)	285 (72%)	281 (78%)	827 (76%)

Data are n (%).

Table 2: Admission to hospital

Supplementary Medications during asthma attack

Magnesium

The additive benefit of MgSO4 in the face of combination therapy with ipratropium bromide and beta$_2$-agonists remains unclear.

Blitz M, Blitz S, Beasely R, Diner BM, Hughes R, Knopp JA, et al. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database of Systematic Reviews 2005, Issue 4. Blitz M, Blitz S, Hughes R, Diner B, Beasley R, Knopp J, et al. Aerosolized magnesium sulfate or acute asthma: a systematic review. Chest 2005;128(1):337-44.

Supplementary Medications during asthma attack - candidates?

- Magnesium
- Heliox
- Leukotriene antagonists
- Methylxanthines
  - Aminophylline (intravenous)
- Iv $Beta_2$- agonist
- ketamine

Supplementary Medications during asthma attack

Heliox- mixture helium and oxygen

Heliox is a mixture of helium and oxygen that reduces air-flow turbulence, compared to air or oxygen

Why it could work:

-Decreasing airway resistance

- Improving flow

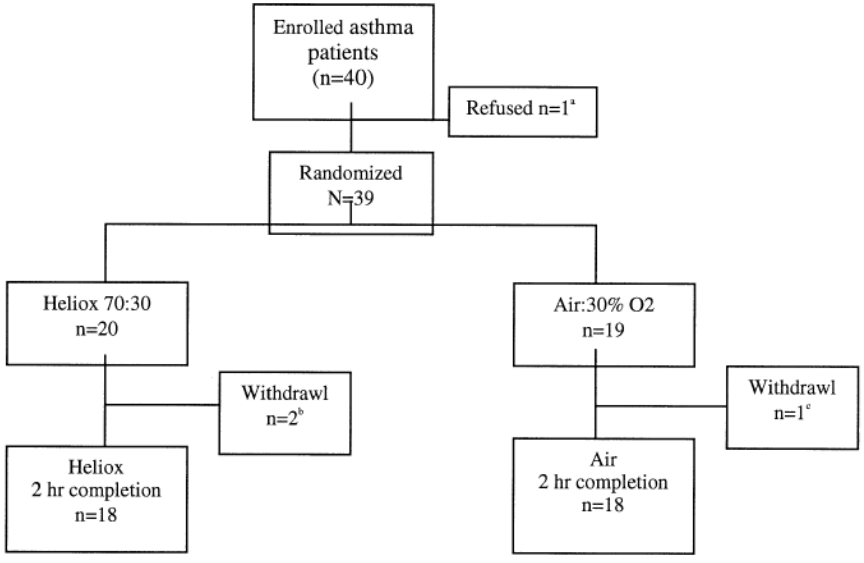
- Aerosol particle delivery to distal airways is increased

(50% increase regardless nebulisation technique)

- reducing work of breathing

Eur Respir Mon 2012; 55: 124–132

PROSPECTIVE RANDOMIZED TRIAL OF HELIOX-DRIVEN CONTINUOUS NEBULIZERS IN THE TREATMENT OF ASTHMA IN THE EMERGENCY DEPARTMENT



Characteristic	Heliox (n = 18)	Air (n = 18)
Mean age (years)	35	39
Sex (M/F)	3/15	5/13
Duration of Sx. (h)	36	28
Previous hospitalizations	13/18	15/18
Previous intubations	5/18	5/18
Beta-2 nebs prior to study	3.1 ± 1.5	3.3 ± 1.8
Ipratropium bromide prior to study	4/18	5/18
Steroids prior to study	18/18	18/18
Initial PEFR L/min*	127 ± 51	112 ± 64
Initial FEV1 L/sc*	0.83	0.96
Initial Borg*	8.3 ± 1.3	7.3 ± 1.6
Initial resp rate/min*	30 ± 15	34 ± 24
Initial SAO_2*(%)	96 ± 3	95 ± 3

- Prospective randomized trial
- Heliox 70:30
- Adults 18-55 years
- Standard therapy: 3 times albuterol (15min apart)
- Peak flow<200

- Exl: COPD;BP<90; heart disease;Sat<90% on 30% oxygen

The Journal of Emergency Medicine, Vol. 22, No. 2, pp. 133–137, 2002

PROSPECTIVE RANDOMIZED TRIAL OF HELIOX-DRIVEN CONTINUOUS NEBULIZERS IN THE TREATMENT OF ASTHMA IN THE EMERGENCY DEPARTMENT

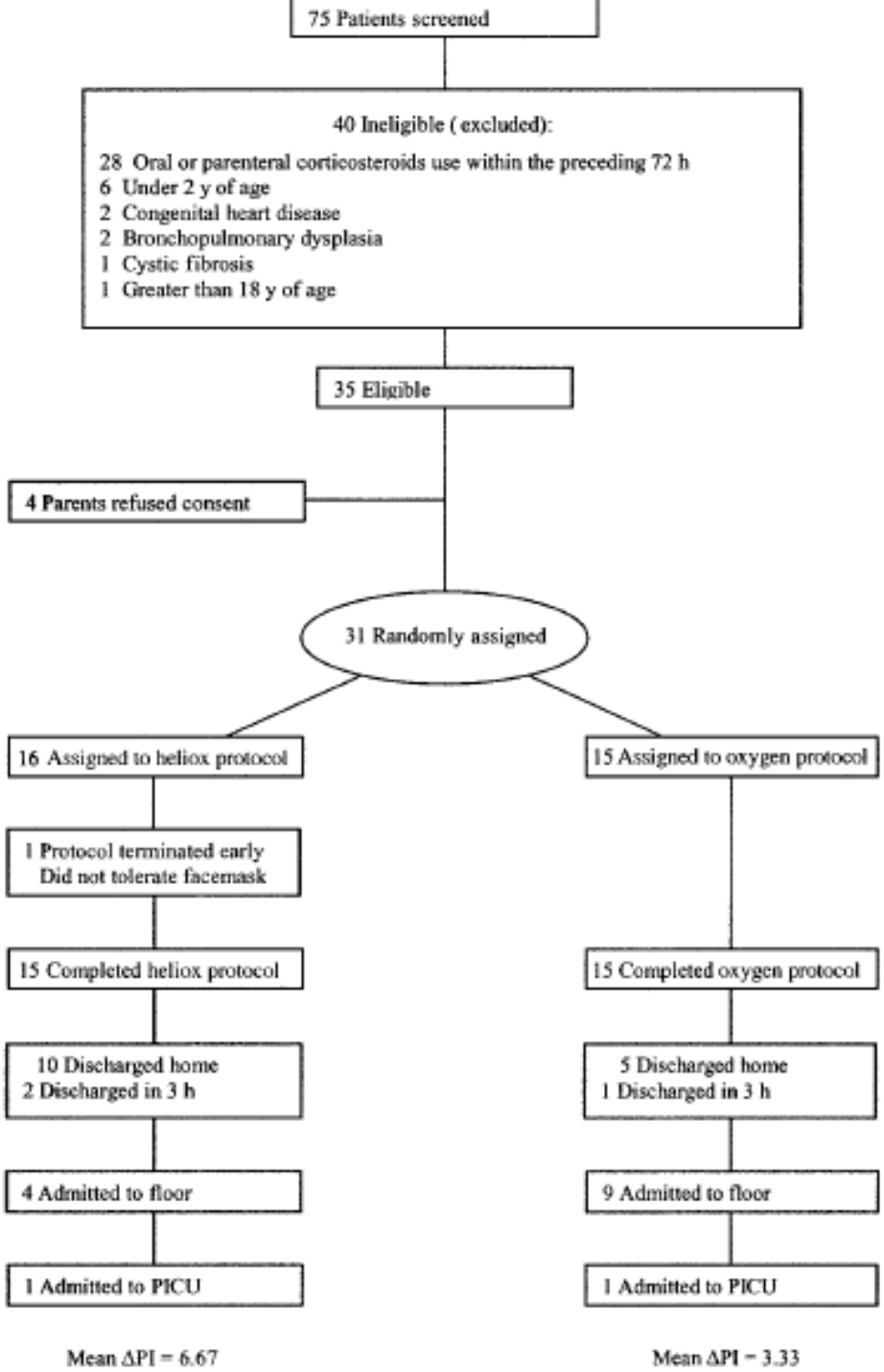
Table 2. Clinical Outcome Variables

	Heliox 70:30			Air/30% O_2			
Variable	Mean T0	Mean T120	Mean Difference (95% CI)	Mean T0	Mean T120	Mean Difference (95% CI)	Between Group Difference (95% CI)
Resp Rate (/min)	29 ± 11	22 ± 3	7.0 (3.1–10)	28 ± 7	21.5 ± 5	6.5 (3.3–8.1)	0.5 (−2.7–3.8)
SaO_2 (%)	94.6 ± 3	95.1 ± 3	0.5 (1.6–0.5)	94.7 ± 2	95.0 ± 2	0.3 (1.6–0.5)	0.2 (−2.0–1.5)
PEFR (L/min)	157 ± 71	220 ± 69	63 (24–93)	159 ± 37	205 ± 63	46 (23–72)	17 (−20–51)
FEV1 (L)	1.13 ± 0.5	1.43 ± 0.5	0.30 (.1–.41)	0.99 ± 0.34	1.26 ± 0.4	0.27 (.07–.33)	0.03 (−0.22–0.30)
Borg	7.0 ± 1.8	3.2 ± 2.7	3.8 (2.2–4.1)	7.1 ± 1.6	4.9 ± 2.5	2.2 (1.5–3.4)	1.6 (0.3–3.0)

Post-Trial Variable	Heliox	Air/30% Oxygen	Between-Group Difference
Admission	50% (9/18)	44.4% (8/18)	5.6% (−27%–38%)
Patient satisfaction 1–10 scale 10 = *very satisfied* 1 = *dissatisfied*	6.6	6.7	0.1 (−1.6–1.8)

No significant difference found between heliox and standard therapy

The Journal of Emergency Medicine, Vol. 22, No. 2, pp. 133–137, 2002



Prospective randomized single blinded study

Children < 6 years

A 70/30 helium/oxygen mixture

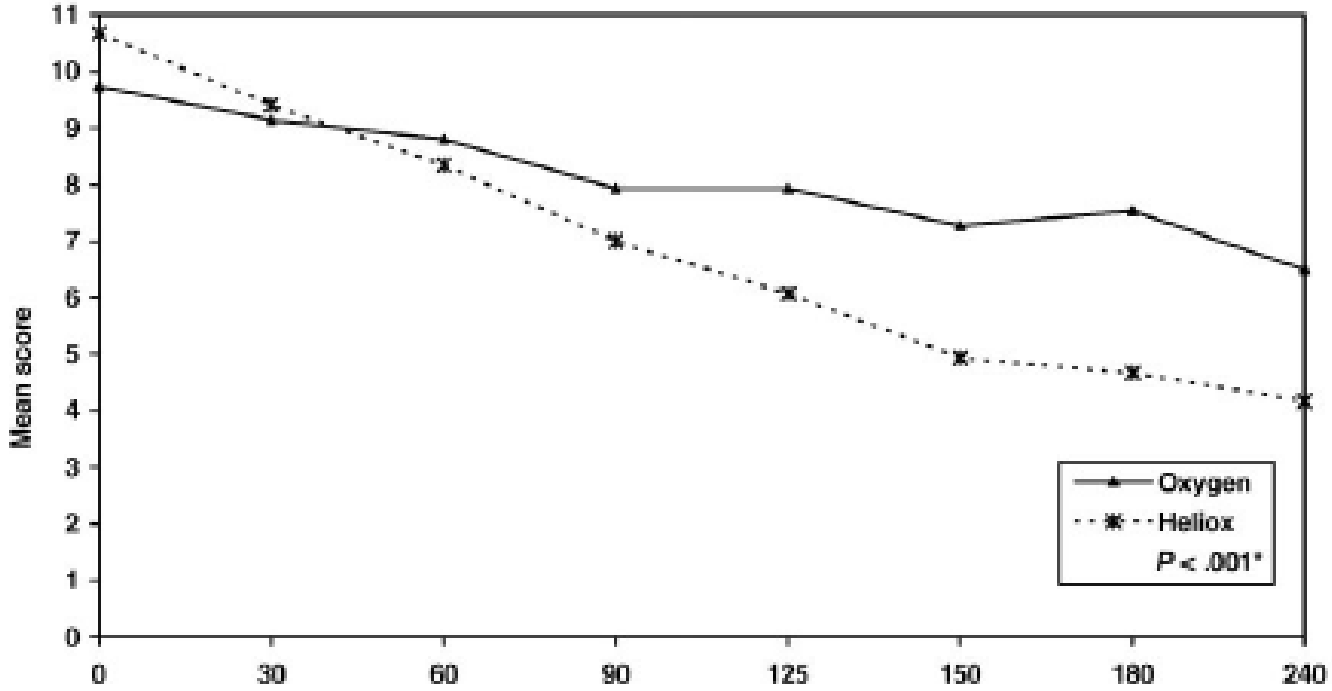
Patient but not doctor blinded for treatment

PEDIATRICS Vol. 116 No. 5 November 2005

TABLE 1. PI: Clinical Asthma Evaluation Score[8–10]

Variables	0	1	2	3
Respiratory rate, respirations per min*	≤30	31–45	46–60	>60
Wheezing†	None	End expiration	Entire expiration	Inspiratory and expiration without stethoscope
Inspiratory/expiratory ratio	2:1	1:1	1:2	1:3
Accessory muscle used	None	+	++	+++
Oxygen saturation	99–100	96–98	93–95	<93

+ indicates mild; ++, moderate; +++, severe.
* For patients ≥6 years of age: through 20 y, score 0; 21–35 y, score 1; 36–50 y, score 2; >50, score 3.
† If no wheezing due to minimal air entry, score 3.



Heliox better in “clinical asthma evaluation score”

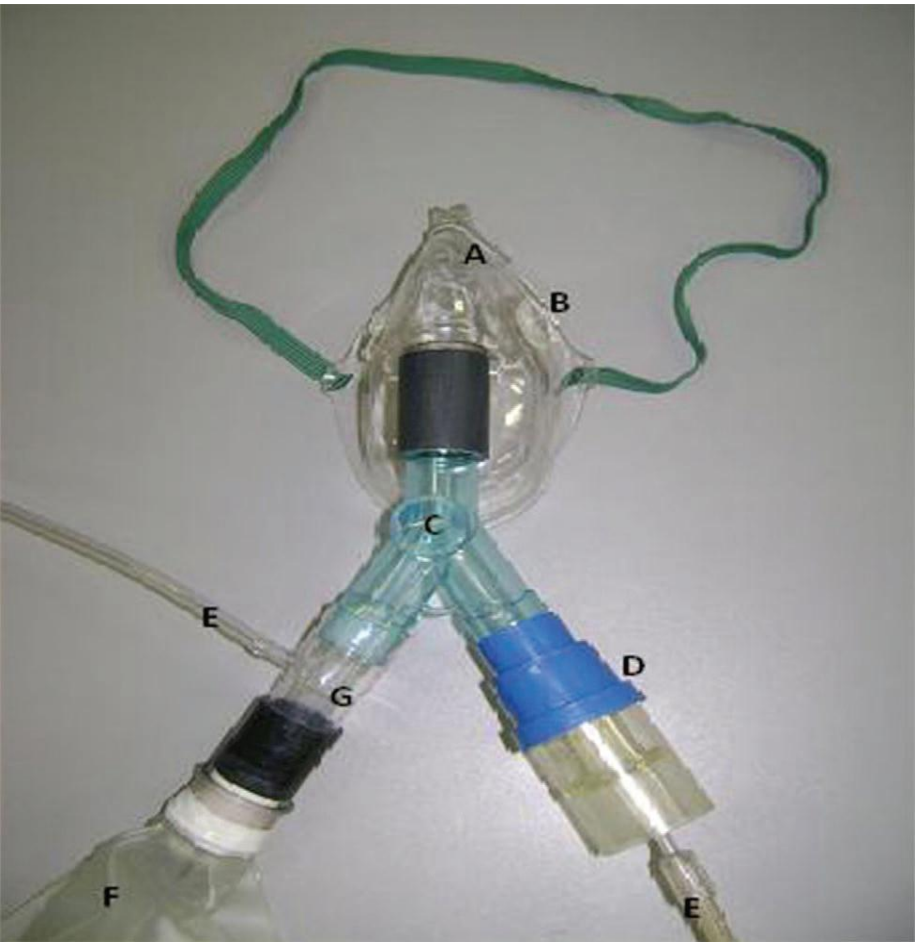
No difference in ED discharge rate

PEDIATRICS Vol. 116 No. 5 November 2005

Supplementary Medications during asthma attack

Heliox and position

Oxygen	Oxygen + Forward-Leaning Posture	Heliox	Heliox + Forward-Leaning Posture



Randomized controlled study with 59 patients; Age 18-65 years
Heliox 80:20
Standard therapy: 2 doses, 20 min apart, fenoterol + ipratropium delivered with a semi-closed valved aerosol reservoir.

FEV1< 60% is a “severe” exacerbation
No collect data on intubation rate or hospitalization

Heliox and position

Primary Outcome: primary outcomes were percentage improvement in FEV1 and PEF.

The post-treatment pulmonary function tests were performed 15 min after the second nebulization.

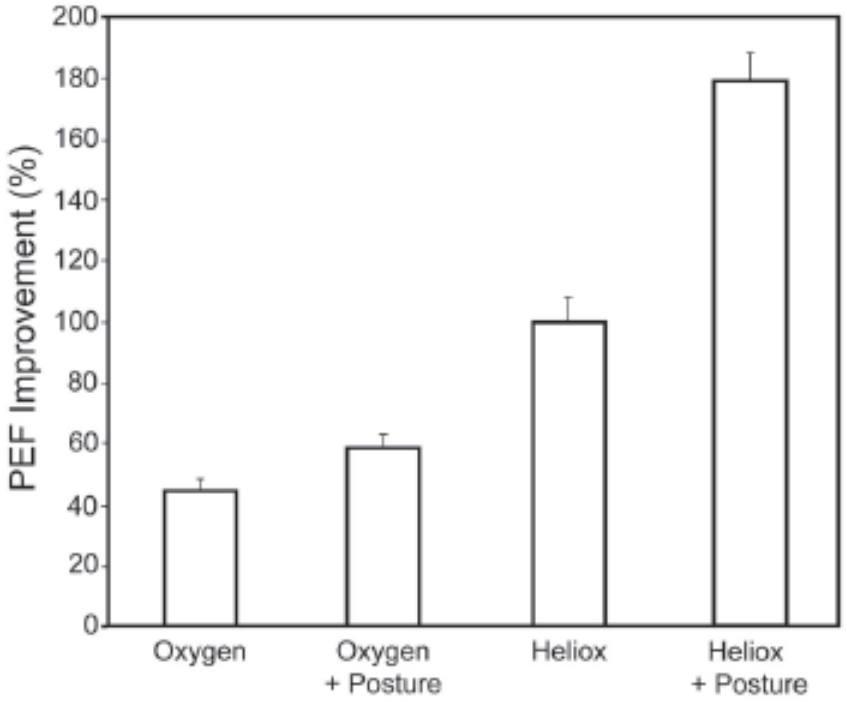


Fig. 3. Post-treatment percentage improvement in peak expiratory flow. All the differences are statistically significant: $P = .04$ for oxygen versus heliox + posture; $P = .03$ for oxygen + posture versus heliox + posture; $P = .02$ for heliox versus heliox + posture.

Table 2. Post-Treatment FEV_1 Improvement

	Oxygen	Oxygen + Forward-Leaning Posture	Heliox	Heliox + Forward-Leaning Posture
FEV_1 improvement, median (IQR), %	38 (27–45)	59 (27–79)*	42 (9–51)	103 (21–120)†‡

* $P = .02$ for oxygen vs oxygen + forward-leaning posture.
† $P = .001$ for heliox + forward-leaning posture vs oxygen.
‡ $P = .03$ for heliox + forward-leaning posture vs heliox.

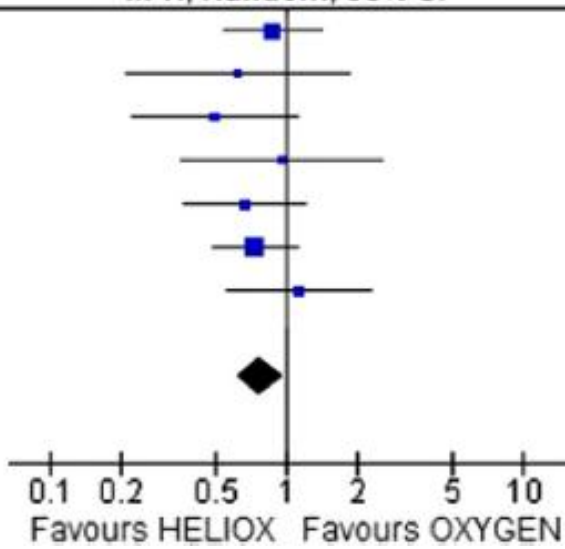
Heliox-driven b2-agonists nebulization for children and adults with acute asthma:

outcome of hospital admissions.

Study or Subgroup	Favours HELIOX Events	Total	Oxygen Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dorfman [18]	12	20	13	19	24.0%	0.88 [0.55, 1.40]
Henderson [17]	5	102	8	102	4.5%	0.63 [0.21, 1.85]
Kim [22]	5	15	10	15	8.3%	0.50 [0.22, 1.11]
Kress [19]	6	23	6	22	5.6%	0.96 [0.36, 2.52]
Lin Lee [23a]	12	40	18	40	15.5%	0.67 [0.37, 1.20]
Rivera [24]	12	20	17	21	31.0%	0.74 [0.49, 1.12]
Rose [20]	9	18	8	18	11.0%	1.13 [0.56, 2.25]
Total (95% CI)		**238**		**237**	**100.0%**	**0.77 [0.62, 0.98]**
Total events	61		80			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.19$, $df = 6$ ($P = 0.79$); $I^2 = 0\%$

Test for overall effect: $Z = 2.17$ ($P = 0.03$)



Same trend for Peak flow measurements (but done only with B2-agonist)

Heliox-driven nebulization therapy has some disadvantages and limitations.
Hypoxia can occur during treatment;
The patient may require a higher fraction of inspired oxygen than the 20% or 30% oxygen
Studies were made with only $beta_2$ agonist.

Ann Allergy Asthma Immunol 112 (2014) 29e34

Supplementary Medications during asthma attack

Heliox

Conclusions :
(small number of studies):

- Heliox seems improve pulmonary function
  - subgroup of patients with the most severe baseline pulmonary function impairment
- Similar trends were found in adults and children
- Most studies were made with only $beta_2$ agonist.
- Heliox is not yet to be suggested as regular medicine in asthma attacks

Heliox for non-intubated acute asthma patients. *Cochrane Database of Systematic Reviews DOI: 10.1002/14651858.CD002884.pub2.*

Supplementary Medications during asthma attack - candidates?

- Magnesium
- Heliox
- Leukotriene antagonists
- Methylxanthines
  - Aminophylline (intravenous)
- Iv $Beta_2$- agonist
- ketamine
- Holding chambers (spacers) versus nebulisers

Supplementary Medications during asthma attack

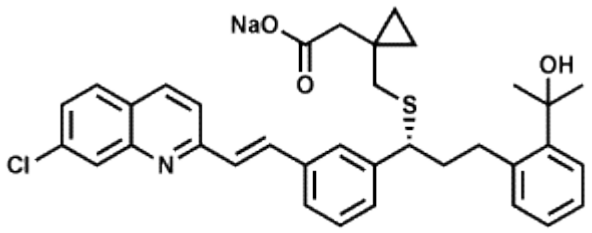
Leukotriene antagonists

Why could it work:

Montelukast is the most commonly used cysteinyl leukotrienes receptor 1 (CysLT-1) antagonist.

It has been shown to improve symptoms and lung function (FEV1) within 15 minutes of administration in chronic asthma with its effects lasting for a period of at least 24 hours

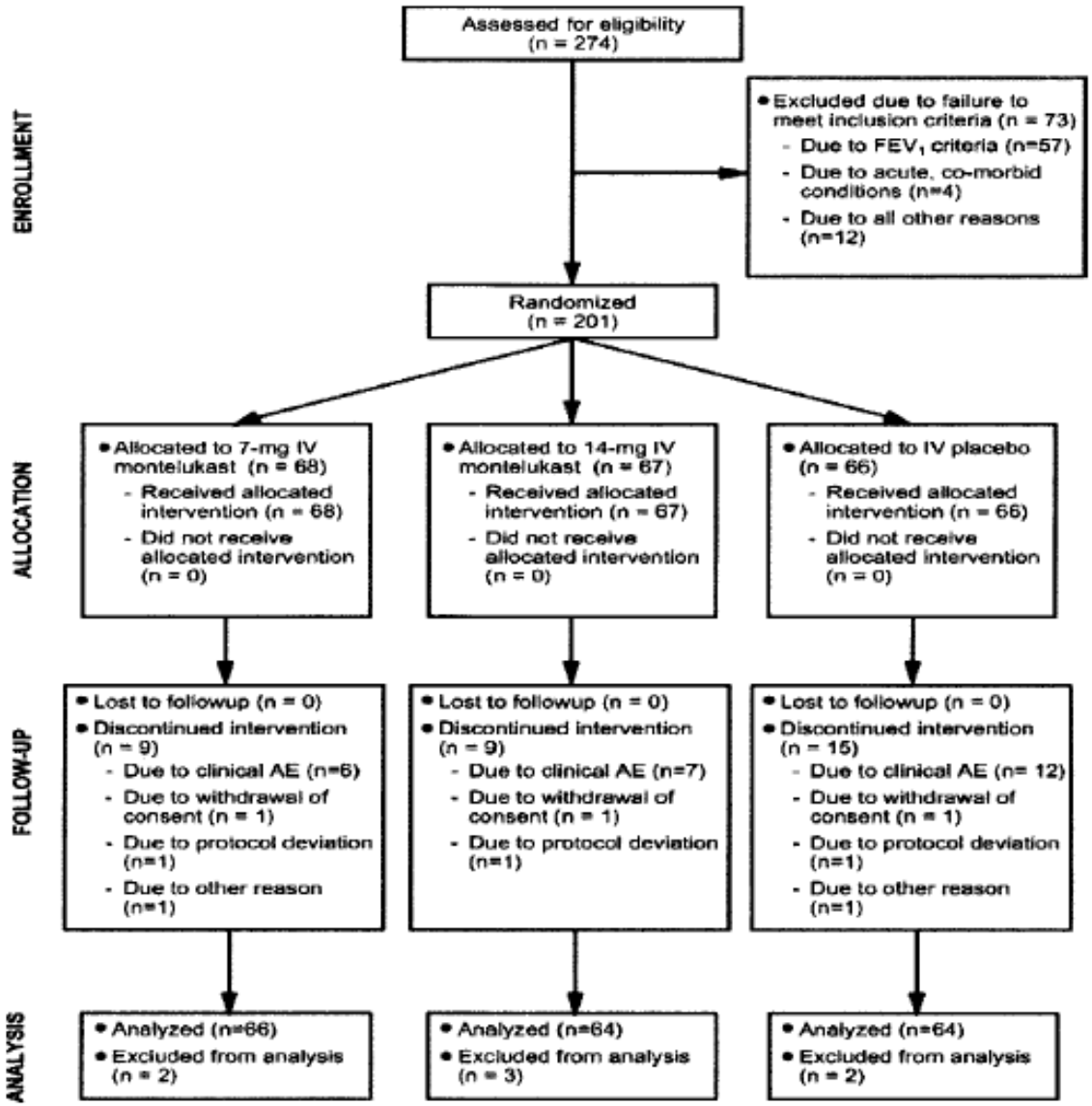
- Corticosteroids do not inhibit leukotriene synthesis so it may work additionally



Montelukast Sodium (Singulair)

Zubairi et al. BMC Pulmonary Medicine 2013, 13:20
Thorax 2000, 55:260–265

A Randomized Controlled Trial of Intravenous Montelukast in Acute Asthma



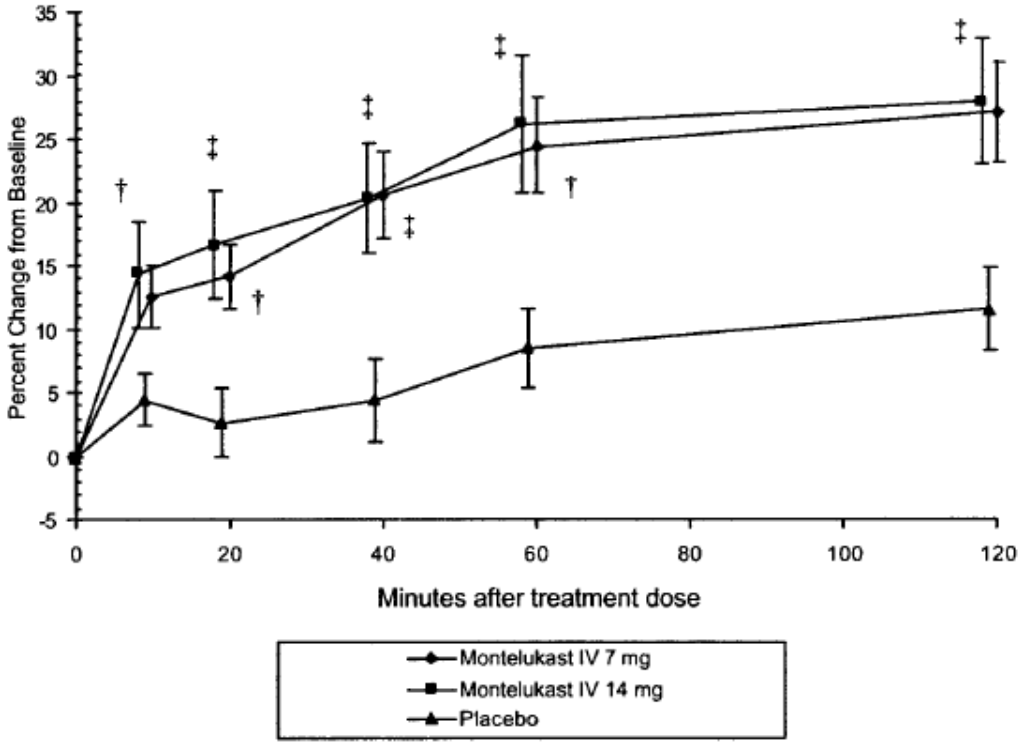
Multicenter, double-blind randomized, placebo-controlled parallel group study
Adults > 18

Consisting of a screening period and an active study period.

Treated 60min:
B_2-agonists (albuterol, 2.5 mg by nebulizer) and oxygen.

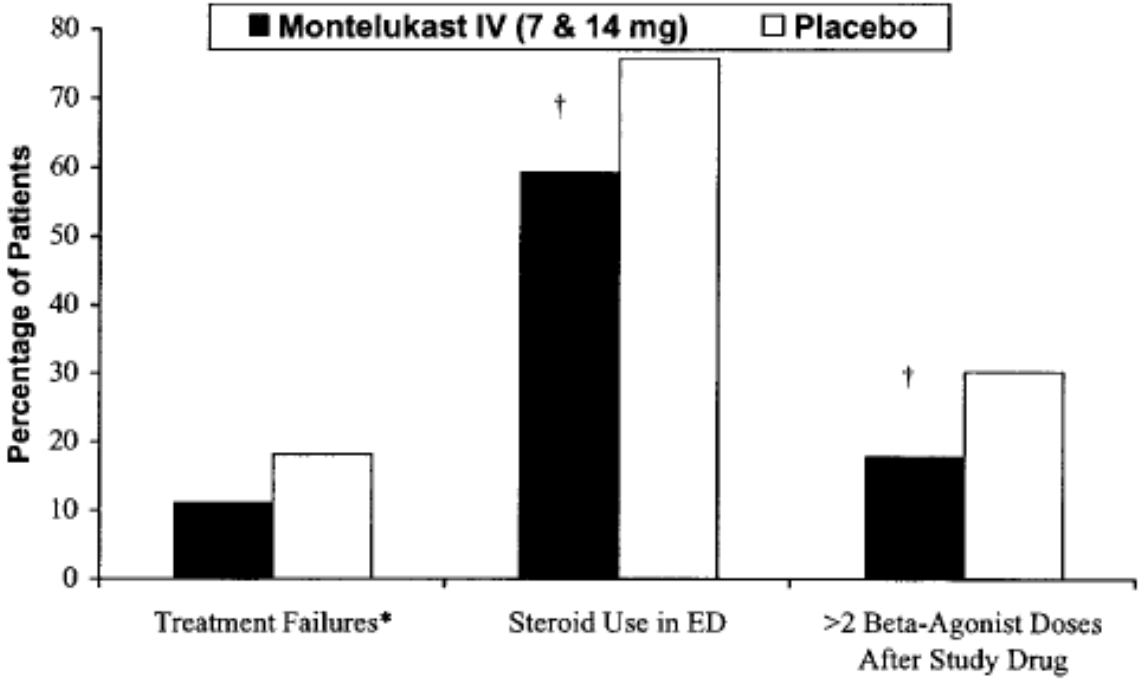
EXCL:
Patients in whom the FEV1>70%
Increased or decreased by greater than or equal to 20%
If a patient needed extended care at 4 h, the protocol ended

Am J Respir Crit Care Med Vol 167. pp 528–533, 2003



The primary endpoint of the study was the average percentage change in FEV1 from pre allocation baseline at 20 minutes after study medication

Authors conclude: intravenous montelukast in addition to standard therapy causes rapid benefit and is well tolerated in adults with acute asthma.



Am J Respir Crit Care Med Vol 167. pp 528–533, 2003

A randomized, placebo-controlled study of intravenous montelukast in children with acute asthma

Double-blind, randomized,multicenter study

6 to 14 years

N=276

Standard treatment

B_2;antichol:pred

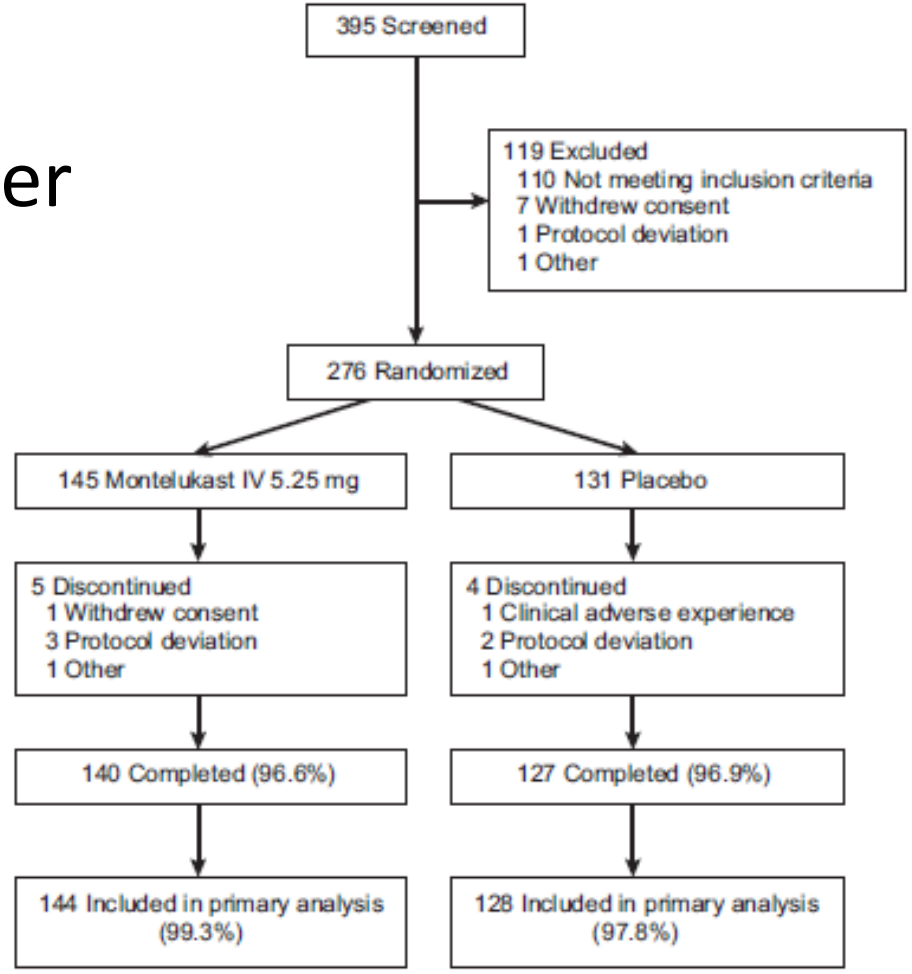


Figure 2. Patient flow through the study. IV indicates intravenous.

Ann Allergy Asthma Immunol. 2010;104:161–171.

A randomized, placebo-controlled study of intravenous montelukast in children with acute asthma

Incl: Patients with an FEV1<75% or less

Primary outcome: The primary efficacy end point was the time-weighted average change in FEV1 from preallocation baseline during the first 60 minutes after drug administration (average FEV1[0-60 min]).

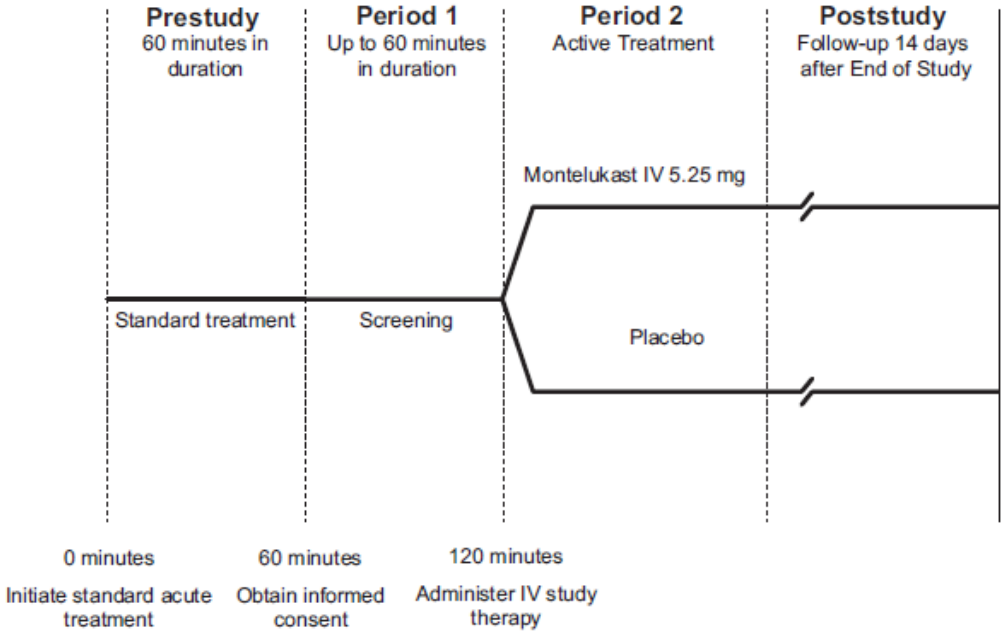


Figure 1. Study diagram. IV indicates intravenous.

Ann Allergy Asthma Immunol. 2010;104:161–171.

A randomized, placebo-controlled study of intravenous montelukast in children with acute asthma

Table 2. Change in FEV_1 From Baseline (Full Analysis Set Population)[a]

FEV_1 measure	Intravenous montelukast, 5.25 mg (n = 145)	Placebo (n = 131)	Difference between montelukast and placebo (95% CI)	*P* value
Time-weighted average $\Delta FEV_{1[0\text{-}60\ min]}$ (primary end point)	0.08	0.07	0.01 (−0.06 to 0.08)	.78
Time-weighted average $\Delta FEV_{1[0\text{-}45\ min]}$	0.07	0.05	0.02 (−0.05 to 0.09)	.61
Average $\Delta FEV_{1[0\text{-}30\ min]}$	0.06	0.05	0.01 (−0.06 to 0.08)	.77
Average $\Delta FEV_{1[0\text{-}15\ min]}$	0.06	0.01	0.04 (−0.02 to 0.11)	.17
Time-weighted average $\Delta FEV_{1[0\text{-}2\ hours]}$	0.10	0.08	0.02 (−0.06 to 0.09)	.68

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ΔFEV_1, time-weighted average change in FEV_1.
[a] All values are expressed as least squares mean change from baseline.

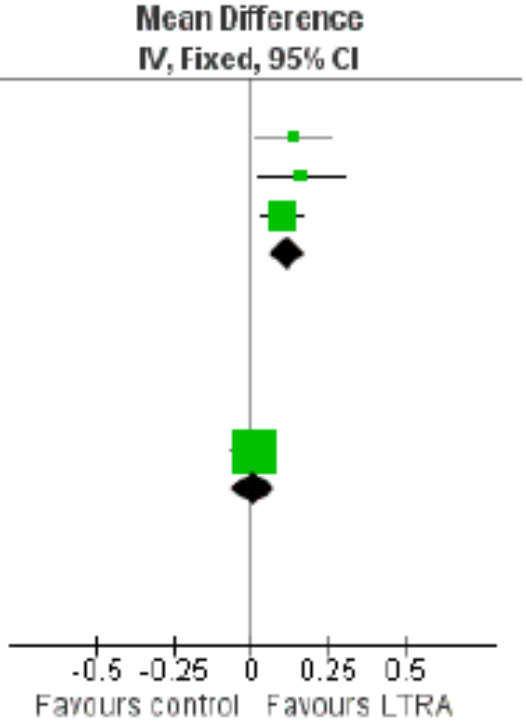
No significant differences between montelukast and placebo for any efficacy end point, including the primary efficacy end point of average FEV

Ann Allergy Asthma Immunol. 2010;104:161–171.

Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children

Figure 6. Forest plot of comparison: 2 Intravenous montelukast in addition to usual care, outcome: 2.3 Change in FEV1 (litres).

Study or Subgroup	LTRA Mean	LTRA SD	LTRA Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
2.3.1 Adults								
Camargo 2003a	0.18	0.27	66	0.04	0.31	32	20.1%	0.14 [0.01, 0.27]
Camargo 2003b	0.2	0.36	63	0.04	0.31	32	16.3%	0.16 [0.02, 0.30]
Camargo 2010	0.32	0.43	287	0.22	0.43	284	63.6%	0.10 [0.03, 0.17]
Subtotal (95% CI)			**416**			**348**	**100.0%**	**0.12 [0.06, 0.17]**
Heterogeneity: Chi² = 0.72, df = 2 (P = 0.70); I² = 0%								
Test for overall effect: Z = 4.10 (P < 0.0001)								
2.3.2 Children								
Morris 2010	0.08	0.3	145	0.07	0.3	131	100.0%	0.01 [-0.06, 0.08]
Subtotal (95% CI)			**145**			**131**	**100.0%**	**0.01 [-0.06, 0.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.28 (P = 0.78)								



Similar results for hospital admissions

Watts K, Chavasse RJPG. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. *Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD006100. DOI: 10.1002/14651858.CD006100.pub2.*

Supplementary Medications during asthma attack

Leukotriene antagonists

Presently, the available evidence does not support routine use of oral LTRAs in acute asthma.

Further studies are required to assess whether intravenous treatment can reduce the risk of hospital admission, and what the most appropriate dose regimen.

Watts K, Chavasse RJPG. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. *Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD006100. DOI: 10.1002/14651858.CD006100.pub2.*

Supplementary Medications during asthma attack - candidates?

- Magnesium
- Heliox
- Leukotriene antagonists
- Methylxanthines
  - Aminophylline (intravenous)
- Iv $Beta_2$- agonist
- ketamine

Supplementary Medications during asthma attack

intravenous aminophylline

- Fifteen studies were included in the previous version of the review.
- There was no statistically significant advantage when adding intravenous aminophylline with respect to hospital admissions
  - (OR 0.58; 95% CI 0.30 to 1.12; 6 studies; n = 315).
- People treated with aminophylline and $beta_2$-agonists had similar peak expiratory flow values compared to those treated with $beta_2$-agonists alone
  - 12 h (MD 8.30 L/min; 95% CI -20.69 to 37.29 L/min)
  - 24 h (MD 22.20 L/min; 95% CI -56.65 to 101.05 L/min).

Nair P, Milan SJ, Rowe BH. Addition of intravenous aminophylline to inhaled beta2-agonists in adults with acute asthma. *Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD002742. DOI: 10.1002/14651858.CD002742.pub2*.

Supplementary Medications during asthma attack intravenous aminophylline

Aminophylline is not significantly better than other bronchodilator drugs, aminophyline has more adverse effects.

Intravenous aminopylline does not seem to have a role in acute asthma treatment

Nair P, Milan SJ, Rowe BH. Addition of intravenous aminophylline to inhaled beta2-agonists in adults with acute asthma. *Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD002742. DOI: 10.1002/14651858.CD002742.pub2*.

Supplementary Medications during asthma attack - candidates?

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  - Aminophylline (intravenous)
- $Beta_2$- agonist (intravenous)
- ketamine

Supplementary Medications during asthma attack

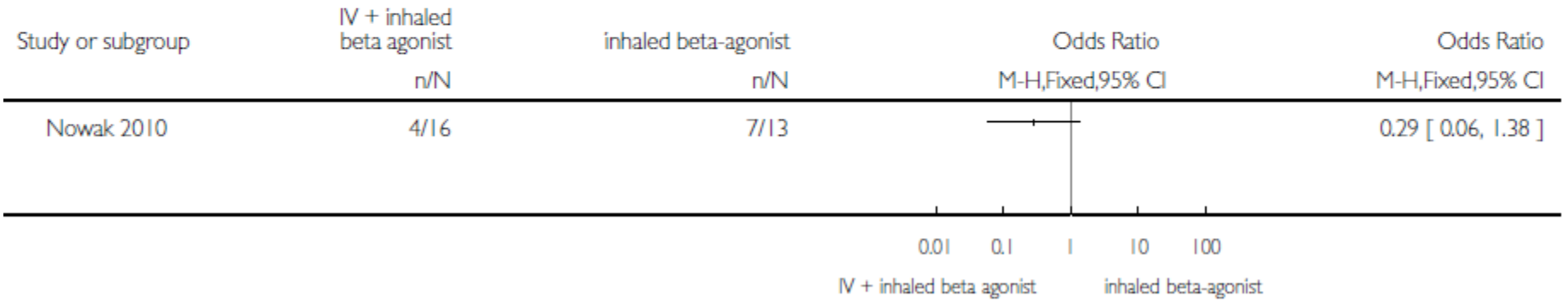
Addition of intravenous beta2-agonists to inhaled beta2- agonists for acute asthma

Analysis 1.1. Comparison 1 IV + inhaled beta agonist vs. inhaled beta-agonist, Outcome 1 Admissions.

Review: Addition of intravenous beta2-agonists to inhaled beta2-agonists for acute asthma

Comparison: 1 IV + inhaled beta agonist vs. inhaled beta-agonist

Outcome: 1 Admissions



1. Further research is required to clarify whether IV beta2-agonists improve outcomes when given in addition to nebulised bronchodilator (beta2-agonists and anticholinergics) and systemic corticosteroid therapy.

Citation: Travers AH, Milan SJ, Jones AP, Camargo Jr CA, Rowe BH. Addition of intravenous beta2-agonists to inhaled beta2-agonists for acute asthma. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD010179. DOI: 10.1002/14651858.CD010179.

Supplementary Medications during asthma attack - candidates?

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- Leukotriene antagonists
- Methylxanthines
  - Aminophylline (intravenous)
- Iv $Beta_2$- agonist
- Ketamine

Supplementary Medications during asthma attack - Ketamine?

- Why could it work?
  - Bronchodilator
    - additional bronchodilation can be obtained by using the dissociative anesthetic ketamine for induction.

Supplementary Medications during asthma attack

Ketamine for management of acute exacerbations of asthma

Children:

- One study enrolling 68 non-intubated children was found eligible for inclusion the rest was case reports in reviews.
  - no significant difference in respiratory rate, oxygen saturation, hospital admission rate (odds ratio (OR) 0.77; 95%CI: 0.23 to 2.58). (Ann Emerg Med. 2005;46:43-50.)

Adults

- no significant difference in respiratory rate, hospital, oxygen saturation, hospital admission rate (Randomized, double-blind, placebo-controlled trial of intravenous ketamine in acute asthma. *Ann Emerg Med* February 1996; 27:170-175.])

Randomized studies with severe acute asthma did not show benefit and does not support the case studies and observational reports showing benefits of ketamine.

Jat KR, Chawla D. Ketamine for management of acute exacerbations of asthma in children. *Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD009293. DOI: 10.1002/14651858.CD009293.pub2.*


Thanks for your attention
Photo by Gazi Yüksel