Acute Asthma in the Emergency Room



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## Potential Conflict of Interest:

In the last three years, I received honoraries for advisor and lectures sponsor by:

> AstraZeneca, GlaxoSmithKline, MerckSharpDhone, and Novartis.



# Levels of evidence

- 1<sup>++</sup> High quality meta-analyses, systematic reviews, or randomised controlled trials (RCTs) with a very low risk of bias
- 1<sup>+</sup> Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
- **1** Meta-analyses, systematic reviews, or RCTs with a high risk of bias

# **Grades of recommendation**

- Relate to strength of evidence, not clinical importance
- Low grade recommendations in important clinical areas should stimulate research

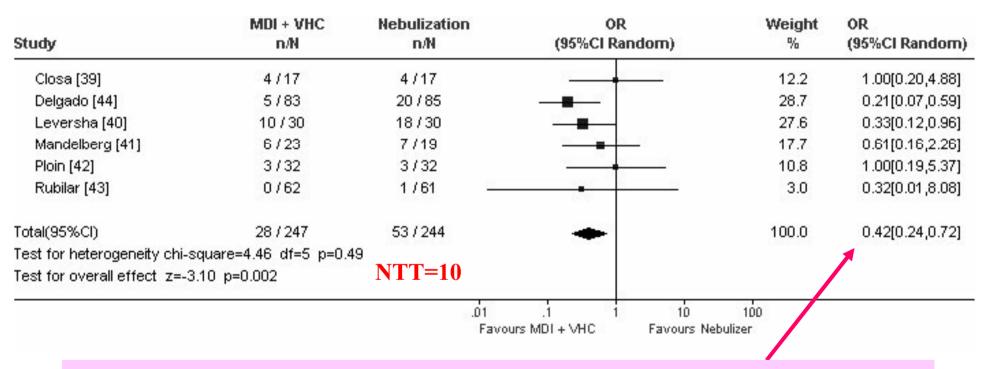
Recommendation	Evidence
Α	At least one 1 <sup>++</sup> directly applicable to target population; or Many studies 1 <sup>+</sup> directly applicable to target population and demonstrating consistency



- ✓ MDI vs. Nebulizer
- ✓ Type of spacer devices
- ✓ Salbutamol vs. Salbutamol+Bromuro Ipatropio
- ✓ Salbutamol vs. Leva-Salbutamol
- ✓ Oral Corticosteroids
- ✓ Systemic vs. Inhaled Corticosteroids
- ✓ Heliox vs. Oxygen for nebulization salbutamol

# $\beta$ -agonists by MDI+VHC vs. by Nebulizers for Acute Exacerbation of Wheezing or Asthma in Children under 5 yrs

6 RCT (n=491)



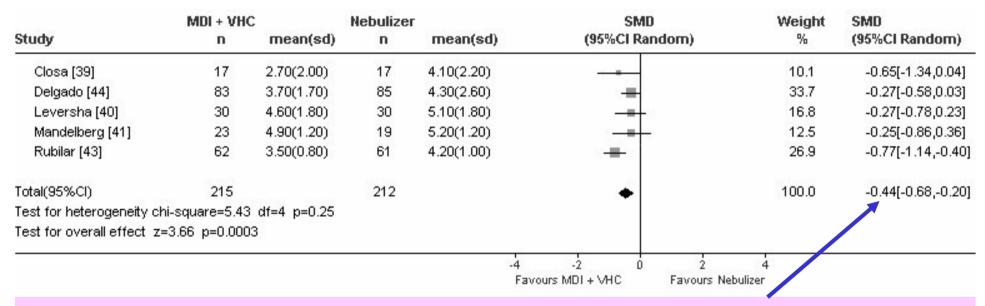
### Need of Hospitalization:

Risk of hospitalization is 58% less using  $\beta$ -agonists by MDI than by nebulizer

Castro-Rodríguez JA & Rodrigo G. J of Pediatr 2004;145:172-7

# $\beta$ -agonists by MDI+VHC vs. by Nebulizers for Acute Exacerbation of Wheezing or Asthma in Children under 5 yrs

### Improvement of clinical score:



Improvement of clinical score is 36% more using  $\beta$ -agonists by MDI than by nebulizer

Castro-Rodríguez JA & Rodrigo G. J of Pediatr 2004;145:172-7



## ✓ MDI vs. Nebulizer

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#### Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children (Review)



N=6 RCT

(n=658)

#### Analysis 01.01. Comparison 01 Home-made spacers versus commercial spacers, Outcome 01 Hospital admission

Review: Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children

Comparison: 01 Home-made spacers versus commercial spacers

Outcome: 01 Hospital admission

Study	Home-made Spacer	Commercial	Relative R	Relative Risk (Fixed) 95% Cl		
Zar 2007	n/N 30/200	n/N 30/200	,cv -		1.00 [ 0.63, 1.59 ]	
			001 0.1 I Favours Home-made	IO IOO Favours Commercial		

#### Analysis 01.02. Comparison 01 Home-made spacers versus commercial spacers, Outcome 02 O2 saturation (SaO2)

Review: Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children Comparison: 01 Home-made spacers versus commercial spacers Outcome: 02 O2 saturation (SaO2)

Study	Home-made N	Mean(SD)	Commercial N	Mean(SD)	Stand	dardise		an Differ 5% Cl	ence (Fxed)	Weight (%)	Standardised Mean Difference (Fixed) 95% Cl
Panicker 2001	30	94.57 (1.90)	(Price)	94.49 (3.58)			٠	1		50.1	0.03 [ -0.48, 0.53 ]
Singhal 2001	31	1.70 (1.90)	29	1.90 (2.36)			+			49.9	-0.09 [ -0.60, 0.41 ]
Total (95% Cl)	61		59				+			100.0	-0.03 [ -0.39, 0.33 ]
Test for heteroger	neity chi-square	=0.11 of=1 p=	0.74 12 =0.0%								
Test for overall ef	fectz=0.18 p	=0.9									
						17	_		-		
					-4.0	-2.0	0	2.0	4.0		
				Favou	rs Com	mercial		Favours	Home-made		



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## Combination of Anticholinergics to β2-agonits in Children with Acute Asthma

#### Less Hospital Admission

N=16 RCT, n=1786 children & adolescents

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% Cl	RR (random) 95% CI
01 Single-dose protocol Schuh [18](SD) Ducharme [21] Subtotal (95% CI) Total events: 32 (Treatment), 36 Test for heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z = 0.47	.05, df = 1 (p = 0.82), l <sup>2</sup> = 0%	19/41 17/151 192	•	0.94 [0.58, 1.53] 0.86 [0.45, 1.66] 0.91 [0.62, 1.35]
02 Multiple-dose protocol (Mode Reisman [14] Peterson [17] Qureshi [22] (Mod) Zorc [23] (Mod) Benito [24] (Mod) Timsit [26] Sharma [27] Subtotal (95% Cl) Total events: 68 (Treatment), 94 Test for heterogeneity: Chi <sup>2</sup> = 2. Test for overall effect: Z = 2.26	2/11 19/82 8/79 24/158 9/28 5/54 1/25 437 (Control) 34, df = 6 (p = 0.89), $l^2 = 0\%$	3/13 25/81 9/84 29/153 17/29 7/63 4/25 448		0.79 [0.16, 3.90] 0.75 [0.45, 1.25] 0.95 [0.38, 2.33] 0.80 [0.49, 1.31] 0.55 [0.30, 1.02] 0.83 [0.28, 2.47] 0.25 [0.03, 2.08] 0.73 [0.55, 0.96]
03 Multiple-dose protocol (Severa Schuh [18] (MD) Qureshi [29] Qureshi [22] (Sev) Zorc [23] (Sev) Benito [24] (Sev) Subtotal (95% CI) Total events: 91 (Treatment), 132 Test for heterogeneity: Chi <sup>2</sup> = 1. Test for overall effect: Z = 3.59	15/40  9/36  51/136  7/22  9/23  257  2 (Control)  .63, df = 4 (p = 0.80), l2 = 0%	19/41 14/31 71/135 12/29 16/22 258		0.81 [0.48, 1.36] 0.55 [0.28, 1.10] 0.71 [0.54, 0.93] 0.77 [0.36, 1.63] 0.54 [0.30, 0.95] 0.69 [0.56, 0.84]
Total (95% CI) Total events: 191 (Treatment), 20 Test for heterogeneity: $Chi^2 = 5$ . Test for overall effect: $Z = 4.09$	.55, df = 13 (p = 0.96), l <sup>2</sup> = 0%	<sup>898</sup> NTT=13		0.73 [0.63, 0.85]

Rodrigo GJ & Castro-Rodriguez JA .Thorax 2005

## Combination of Anticholinergics to β2-agonits in Children with Acute Asthma

### Higher FEV1 improvement

Study		Treatment		Control		SMD (rai		SMD (random)
or sub-category	Ν	mean (SD)	Ν	mean (SD)		95%	Cl	95% CI
01 One or two doses								
Beck [12]	13	-20.40 (19.50)	12	-4.10 (6.20)				-1.07 [-1.92, -0.22]
Watson [15]	16	-89.50 (13.20)	16	-80.00 (14.00)				-0.68 [-1.40, 0.03]
Phanichyakam [16]	10	-36.40 (36.00)	10	-22.00 (38.30)				-0.37 [-1.26, 0.51]
Schuh [18] (SD)	30	-22.10 (15.30)	41	-15.00 (13.80)			_	-0.49 [-0.96, -0.01]
Subtotal (95% CI)	69		79					-0.60 [-0.94, -0.27]
Test for heterogeneity: Chi <sup>2</sup> =	1.70, df	= 3 (p = 0.64), l <sup>2</sup> = 0%				•		
Test for overall effect: $Z = 3.5$	4 (p = 0)	.0004)				-		
02 More than two doses								
Keisman [14]	11	-35.00 (17.00)	13	-22.00 (13.00)		_		-0.84 [-1.68, 0.00]
Schuh [18] (MD)	39	-23.40 (20.60)	38	-13.20 (13.30)				-0.58 [-1.04, -0.12]
Sienra [25]	15	-38.00 (18.00)	15	–19.00 (12.00)				–1.21 [–2.00, –0.42]
Sharma [27]	25	-35.00 (4.90)	25	–30.00 (3.15)				–1.19 [–1.80, –0.59]
Subtotal (95% CI)	90		91					-0.88 [-1.22, -0.55]
Test for heterogeneity: Chi <sup>2</sup> =	3.36, df	= 3 (p = 0.34), l <sup>2</sup> = 10.7%				-		
Test for overall effect: $Z = 5.2$	2 (p < 0.	00001)						
Total (95% CI)	159		170					-0.75 [-0.97, -0.52]
Test for heterogeneity: Chi <sup>2</sup> =		$= 7 (p = 0.49), l^2 = 0\%$				•		
Test for overall effect: $Z = 6.4$								
	(p < 0)				I	,	1 1	
					_4 _	-2 0	2 4	
					- <b>T</b>	2 0	- 4	

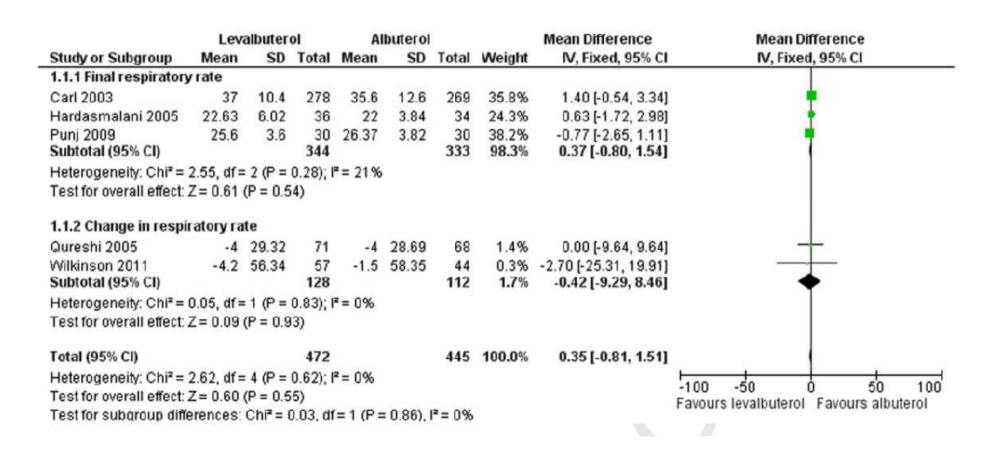
Rodrigo GJ & Castro-Rodriguez JA .Thorax 2005



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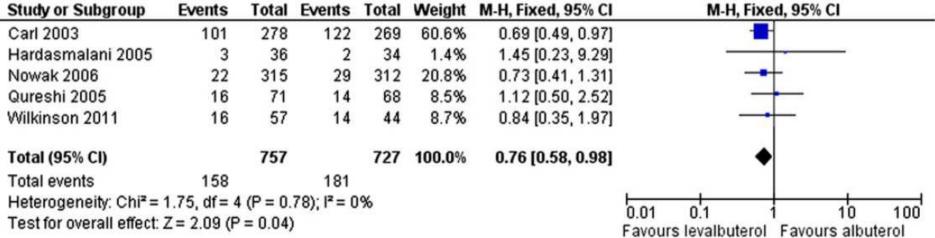
# Levalbuterol vs. Albuterol for Acute Ashtma

N=7RCTs, n=1625 (only 1 in adults Nowak)



Ram K, Khairwa A. Pulm Pharm & Therap 2013

	LGV	ainarci v			inutero			mean pinerence	mean Direi ence
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
1.2.1 Final oxygen sa	turation								
Carl 2003	95.6	2.8	278	95.9	2.7	269	71.8%	-0.30 [-0.76, 0.16]	
Hardasmalani 2005	97.95	1.54	36	98.23	1.76	34	25.3%	-0.28 [-1.06, 0.50]	•
Punj 2009 Subtotal (95% CI)	98.23	11.01	30 344	97.73	7.22	30 333	0.7% 97.8%	0.50 [-4.21, 5.21] -0.29 [-0.68, 0.11]	
Heterogeneity: Chi <sup>2</sup> =	0.11, df=	2 (P = 0	.95); P	<sup>2</sup> = 0%					
Test for overall effect:	Contraction of the second								
1.2.2 Change in oxyg	en satura	ation							
Qureshi 2005	1	14.66	71	1	10.76	68	0.8%	0.00 [-4.26, 4.26]	+
Wilkinson 2011	1	7.91	57	1.6	8.71	44	1.4%	-0.60 [-3.89, 2.69]	+
Subtotal (95% CI)			128			112	2.2%	-0.38 [-2.98, 2.23]	•
Heterogeneity: Chi <sup>2</sup> =	0.05, df=	: 1 (P = 0	.83); 1	²= 0%					
Test for overall effect:	Z = 0.28	(P = 0.78	))						
Total (95% CI)			472			445	100.0%	-0.29 [-0.68, 0.10]	
Heterogeneity: Chi <sup>2</sup> =	0.16, df=	= 4 (P = 1	.00); 12	² = 0%					-100 -50 0 50 100
Test for overall effect:									-100 -50 0 50 100 Favours levalbuterol Favours albuterol
Test for subgroup diff	erences:	Chi <sup>2</sup> = 0	00, df	= 1 (P :	= 0.95),	l <sup>2</sup> = 0%			
	Leval	outerol	A	lbuter	ol		Od	ds Ratio	Odds Ratio
tudy or Subgroup	Events	s Tota	al Ev	ents	Total	Weight	t M-H, I	Fixed, 95% Cl	M-H, Fixed, 95% Cl
arl 2003	101	1 27	8	122	269	60.6%	6 0.6	9 [0.49, 0.97]	



ig. 5. Pooled odds ratio for hospital admission rate of eligible studies comparing levalbuterol versus albuterol in acute asthma.



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#### Efficacy of Oral Corticosteroids in the Treatment of Acute Wheezing Episodes in Asthmatic Preschoolers

#### 2a. Overall hospital admissions SC. **Risk Ratio** Placebo **Risk Ratio** Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI Grant 1995 9 19 7 27 25.1% 1.83 [0.83, 4.04] б Oommen 2003 52 2 69 13.4% 3.98 [0.84, 18.93] 11 36 Scarfone 1993 19 39 29.2% 0.63 [0.35, 1.13] 8 39 Tal 1990 15 35 26.5% 0.48 [0.23, 0.99] Webb 1986 1 29 1 27 5.8% 0.93 [0.06, 14.16] Total (95% CI) 175 197 100.0% 1.00 [0.49, 2.05] Total events 35 44 Heterogeneity: Tau<sup>2</sup> = 0.37; Chi<sup>3</sup> = 10.81, df = 4 (P = 0.03); l<sup>3</sup> = 63% 0.01 0.1 100 10 Test for overall effect: Z = 0.00 (P = 1.00) **Favours OCS** Favours Placebo 2b. Outpatient studies and hospital admissions Placebo **Risk Ratio Risk Ratio** SC Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI

Grant 1995	9	19 7	27	67.7%	1.83 [0.83, 4.04]		
Oommen 2003	6	52 2	69	20.1%	3.98 [0.84, 18.93]		
Webb 1986	1	29 1	27	12.1%	0.93 [0.06, 14.16]		
Total (95% CI)	10	00	123	100.0%	2.15 [1.08, 4.29]		•
Total events	16	10					
Heterogeneity: Chi2 =	= 1.12, df = 2	(P = 0.57); I	2 = 09	£		has di	10 100
Test for overall effect	t: Z = 2.18 (P	= 0.03)				Favours OCS	Favours Placebo

#### 2c. ED studies and hospital admissions

		122111111		bo	1001201201	Risk Ratio	Risk F	
itudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	d, 95% CI
icarfone 1993	11	36	19	39	54.9%	0.63 [0.35, 1.13]		
al 1990	8	35	15	35	45.1%	0.53 [0.26, 1.09]		
fotal (95% CI)		71		74	100.0%	0.58 [0.37, 0.92]	•	
fotal events	19		34					
feterogeneity: Chi <sup>2</sup> =	0.12, df	= 1 (P)	= 0.73);	$t^2 = 0\%$			0.01 0.1	10 10
est for overall effect:	Z = 2.31	1 (P = 0	0.02)					10 10 Favours Placebo

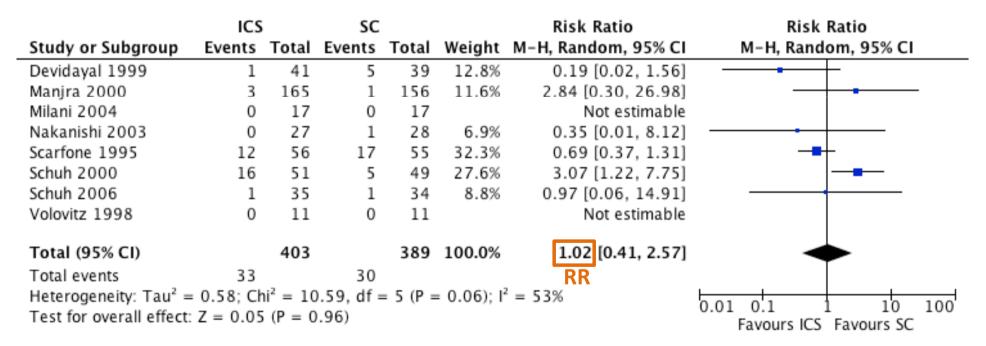


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# Inhaled vs. Systemic Corticosteroids for Acute Asthma in Children

#### N=8 RCT (2-18yrs), n=797

### **Hospitalizations**

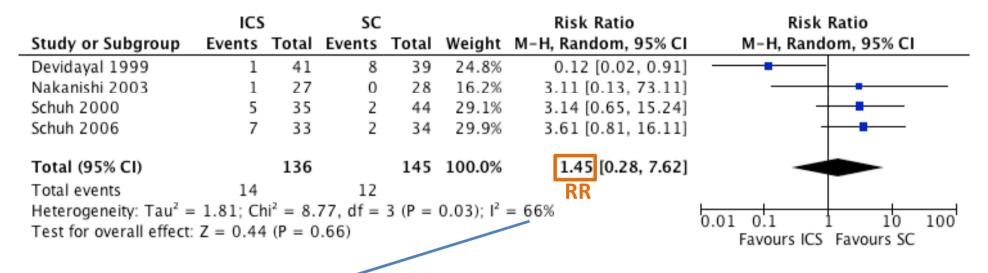


Beckhaus A, Riutort MC, Castro-Rodriguez JA. Pediatr Pulmonol 2014

## Inhaled vs. Systemic Corticosteroids for Acute Asthma in Children

#### N=8 RCT (2-18yrs), n=797

### Need of additional systemic corticosteroids



- NBZ (1 RCT) → RR: 0.12 (95% CI: 0.02 to 0.91), I<sup>2</sup>=0%
- pMDI (3 RCT) → RR: 3.35 (95% CI: 1.20 to 9.35), I<sup>2</sup>=0%

Beckhaus A, Riutort MC, Castro-Rodriguez JA. Pediatr Pulmonol 2014

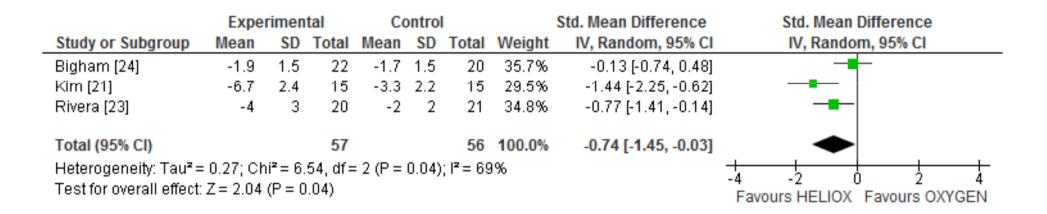


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# Heliox- driven $\beta$ 2-AGONISTS Nebulization for children & adults with acute asthma: a sistematic review/meta-analysis

11 RCT (3 RCT children, n=113) mean 120 min He 70:30

#### Mean change in Asthma or pulmonary composite score



# Heliox- driven $\beta$ 2-AGONISTS Nebulization for children & adults with acute asthma: a sistematic review/meta-analysis

#### 11 RCT (3 RCT children, n=113) mean 120 min He 70:30

#### Hospitalizations

	Favours HE	LIOX	Oxyg	en		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
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]	4	15	10	15	6.4%	0.40 [0.16, 1.00]	
Kress [19]	6	23	6	22	5.7%	0.96 [0.36, 2.52]	+
Lin Lee (a) [23]	12	40	18	40	15.6%	0.67 [0.37, 1.20]	+
Rivera [24]	12	20	18	21	33.5%	0.70 [0.47, 1.04]	
Rose [20]	9	20	8	19	10.4%	1.07 [0.52, 2.19]	
Total (95% CI)		240		238	100.0%	0.75 [0.59, 0.94]	•
Total events	60		81				
Heterogeneity: Tau² =	= 0.00; Chi <b>²</b> =	3.84, df	= 6 (P = 0	0.70); <mark>I</mark> ≊	= 0%		0.05 0.2 1 5 20
Test for overall effect:	Favours HELIOX Favours OXYGEN						

# **Conclusions:** Management Acute Asthma

-Salbutamol by MDI is better than by nebulizer

-Valvulate and non-valvulate spacer device are similar

-Salbutamol is equal to Leva-salbutalmol

-Bromuro ipatropio + salbutamol is better than salbutamol (moderate/severe exacerbations)

-Oral Corticosteroids is effectiveness only at the ED (not a home)

-Inhaled Corticosteroids is similar to systemic corticosteroids

-Nebulization salbutamol w/Heliox is better than w/oxygeno (severe exacerbations)



Muito Obrigado Muchas Gracias Thanks!

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