

Why Don't Pharmacological Agents Work Well in Treatment of Asthma in Young Children

Review of Efficacy of Current Pharmacological Agents in Very Young Children with Recurrent Wheeze

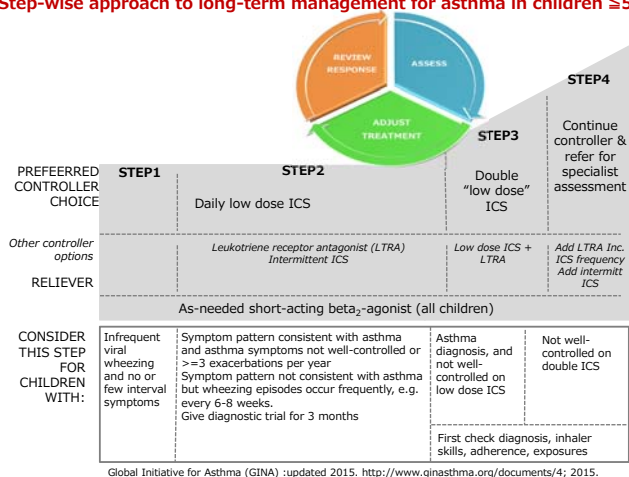
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Diagnosis of asthma/wheezing in young children is not easy

- Recurrent wheezing occurs in a large proportion of children 5 years and younger, typically with viral upper respiratory tract infections. Deciding when this is the initial presentation of asthma is difficult.
- Previous classifications of wheezing phenotypes (episodic wheeze and multiple-trigger wheeze; or transient wheeze, persistent wheeze and late-onset wheezing) is more likely if they have:
 - Wheezing or coughing that occurs with exercise, laughing or crying in the absence of an apparent respiratory infection
 - A history of other allergic disease (eczema or allergic rhinitis) or asthma in first-degree relatives
 - Clinical improvements during 2-3 months of controller treatment, and worsening after cessation.

the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) :updated 2015. <http://www.ginasthma.org/documents/4>; 2015.

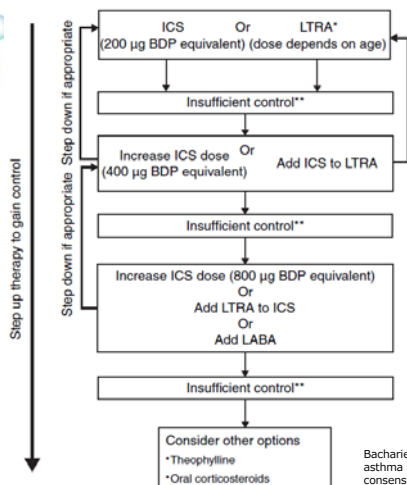
Step-wise approach to long-term management for asthma in children ≤5



Low daily doses of ICS for children 5 years and younger

Drug	Low daily dose (µg)
Beclomethasone dipropionate (HFA)	100
Budesonide pMDI + spacer	200
Budesonide nebulized	500
Fluticasone propionate (HFA)	100
Ciclesonide	160
Mometasone furoate	Not studied below age 4
Triamcinolone acetonide	Not studied

Global Initiative for Asthma (GINA) :updated 2015. <http://www.ginasthma.org/documents/4>; 2015.



Bacharier Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008; 63: 5-34.

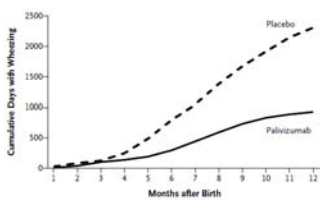
Clinical Questions

- Does asthma medication prevent recurrent wheeze after RSV infection?
- Does asthma medication prevent the development of asthma after RSV infection?
- Is asthma medication effective for preschool children with recurrent wheeze?
- Is intermittent asthma medication effective for recurrent wheeze/asthma?

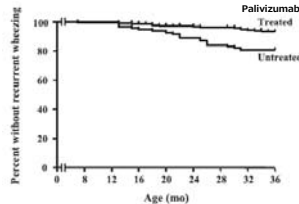
CQ1: Does asthma medication prevent recurrent wheeze after RSV infection?

Background

- RSV bronchiolitis may be causally related to recurrent wheeze in early life in late preterm infants.



Blanken MO, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med* 2013; 368: 1791-1799.



Yoshihara S, et al. Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants. *Pediatrics* 2013; 132: 811-818.

CQ1: Does asthma medication prevent recurrent wheeze after RSV infection?

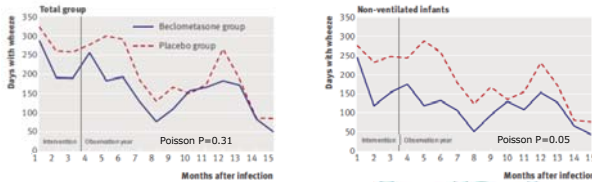
- ICS

CQ1-1: Does ICS prevent recurrent wheeze after RSV infection?

Patients: 243 previously healthy infants (126 boys, 117 girls) aged less than 13 months and admitted to hospital with respiratory syncytial virus infection.

Interventions: 200 µg BDP (HFA) twice daily or matched placebo administered by a pressurised metered dose inhaler and a spacer during the first 3 months after hospital admission.

Primary outcome: the number of days with wheeze in the year after the three month intervention period.



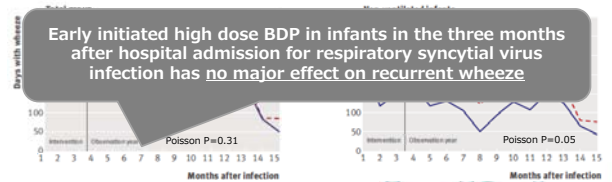
Ermers MJ, et al. The effect of high dose inhaled corticosteroids on wheeze in infants after respiratory syncytial virus infection: randomised double blind placebo controlled trial. *BMJ* 2009; 338: b897.

CQ1-1: Does ICS prevent recurrent wheeze after RSV infection?

Patients: 243 previously healthy infants (126 boys, 117 girls) aged less than 13 months and admitted to hospital with respiratory syncytial virus infection.

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CQ1: Does asthma medication prevent recurrent wheeze after RSV infection?

- Leukotriene receptor antagonist (LTRA)

CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?

Patients: 3- to 24-month-old children hospitalized for a first or second episode of physician-diagnosed, laboratory-confirmed RSV bronchiolitis (n=979).

Interventions: montelukast or placebo for 4 weeks (period I) and 20 weeks (period II).

Primary outcome: percentage symptom-free days (%SFD; day with no daytime cough, wheeze, and shortness of breath, and no nighttime cough).

Biggaard H, et al. Study of montelukast for the treatment of respiratory symptoms of post-respiratory syncytial virus bronchiolitis in children. *Am J Respir Crit Care Med* 2008; 178: 854-860.

CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?

Patient Characteristic	Montelukast		
	Placebo (n = 318)	4 mg (n = 315)	8 mg (n = 319)
Age, mo: mean ± SD (range)	7.4 ± 4.6 (2-23)	7.8 ± 4.4 (3-23)	8.1 ± 4.7 (2-23)
Sex, n (%)			
Male	189 (59.4)	185 (58.7)	184 (57.7)
Race, n (%)			
White	133 (41.8)	120 (38.1)	126 (39.5)
Black	16 (5.0)	20 (6.3)	23 (7.2)
Hispanic	103 (32.4)	115 (36.5)	113 (35.4)
Asian	43 (13.5)	40 (12.7)	46 (14.4)
Other	23 (7.2)	20 (6.3)	11 (3.4)
Patients positive for RAST,* no. (%)	127 (46.5)	122 (46.7)	137 (53.3)
Patients staying in the hospital ≥ 24 h, no. (%)	298 (93.7)	300 (95.2)	301 (94.4)
Duration of hospital stay (h) for patients hospitalized < 24 h	9.8 ± 8.6	9.8 ± 7.7	10.4 ± 8.2
Respiratory severity score for patients hospitalized < 24 h, 0-8 scale	5.5 ± 1.1	5.8 ± 1.0	6.0 ± 1.0
Episode of bronchiolitis, n (%)			
First episode	274 (86.2)	264 (83.8)	262 (82.1)
Second episode	28 (0.09)	35 (0.11)	34 (0.11)
Percent oxygen saturation†	94.7 ± 3.8	94.3 ± 4.1	94.3 ± 4.4
Respiratory rate, breaths/min	41.5 ± 10.6	42.9 ± 11.2	42.1 ± 10.5
Patients needing oxygen during hospitalization, no. (%)	84 (26.5)	105 (33.4)	105 (33.0)
Patients receiving corticosteroids during hospitalization, no. (%)	76 (23.9)	74 (23.5)	72 (22.6)

Biggaard H, et al. Study of montelukast for the treatment of respiratory symptoms of post-respiratory syncytial virus bronchiolitis in children. *Am J Respir Crit Care Med* 2008; 178: 854-860.

CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?

EFFICACY RESULTS DURING THE 4-WEEK (PERIOD I) AND 24-WEEK (PERIODS I+II) TREATMENT PERIODS

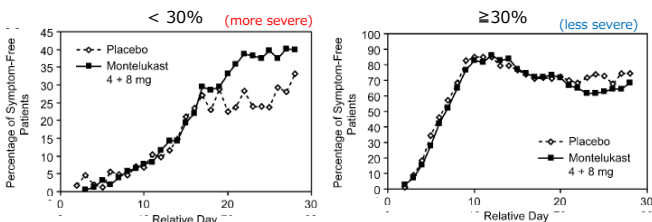
	Placebo (n = 318)	Montelukast, 4 mg (n = 315)	Montelukast, 8 mg (n = 319)
Period I			
Symptom-free days, %	37.0 ± 30.7	38.6 ± 30.4	38.5 ± 29.9
Bronchiolitis-free days, %	32.5 ± 29.5	33.8 ± 29.3	33.8 ± 28.8
Cough-free days, %	40.0 ± 30.9	40.8 ± 30.9	41.8 ± 30.1
Days without β-agonist use, %	66.2 ± 32.1	63.6 ± 31.2	66.2 ± 29.2
Average of individual daily symptom scores	0.63 ± 0.51	0.59 ± 0.48	0.60 ± 0.47
Periods I + II			
Symptom-free days, %	58.2 ± 27.8	60.8 ± 27.1	60.7 ± 27.2
Bronchiolitis-free days, %	55.7 ± 28.4	58.4 ± 27.4	58.1 ± 28.0
Average of individual daily symptom scores	0.39 ± 0.39	0.34 ± 0.35	0.37 ± 0.37
Patients with exacerbations, %	33.3	31.4	31.7
Patients with systemic corticosteroid use, %	19.2	22.5	19.4
Patients with health care resource use, %	54.1	55.9	50.5

Biggaard H, et al. Study of montelukast for the treatment of respiratory symptoms of post-respiratory syncytial virus bronchiolitis in children. *Am J Respir Crit Care Med* 2008; 178: 854-860.

CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?

Post-hoc analysis

percentage of symptom-free days over Week 2



Biggaard H, et al. Study of montelukast for the treatment of respiratory symptoms of post-respiratory syncytial virus bronchiolitis in children. *Am J Respir Crit Care Med* 2008; 178: 854-860.

CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?

Patients: 200 infants (age, 6-24 months) hospitalized with their first episode of acute RSV bronchiolitis

Interventions: **montelukast** or **placebo** for 3 months (12 weeks)

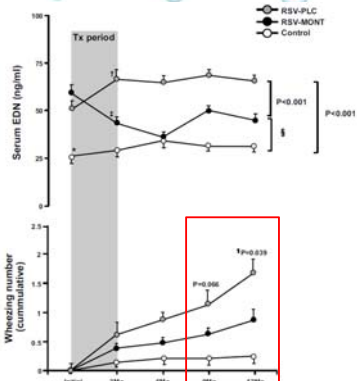
Primary outcome: effect of montelukast on eosinophil degranulation in RSV bronchiolitis by measuring **EDN levels**.

Secondary outcome: recurrent wheezing episodes

	RSV-MONT (n = 79)	RSV-PLC (n = 71)	Control (n = 28)
Age, months*	13.2 (6-23)	15.1 (7-24)	14.0 (6-22)
Sex, male:female	54:25	46:25	12:16
Atopic heredity, %	46	38	36
Atopic dermatitis, %	18.5	16.2	0.0
Blood eosinophils, mm ³ †	190 (11-809)	168 (39-900)	91 (49-334)
Symptom score, 0-10 [†]	6.1 (4-9)	5.9 (4-9)	-
Therapy			
O ₂ , %	25	28	-
β ₂ agonist, %	71	67	-
Ventilator, %	0	0	-

Kim CK, et al. A randomized intervention of montelukast for post-bronchiolitis: effect on eosinophil degranulation. *J Pediatr* 2010; 156: 749-754.

CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?



Kim CK, et al. A randomized intervention of montelukast for post-bronchiolitis: effect on eosinophil degranulation. *J Pediatr* 2010; 156: 749-754.

CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?

Patients: 58 patients (aged <24 months) hospitalized with a first episode of RSV bronchiolitis

Interventions: **montelukast** or **placebo** for 3 months (12 weeks)

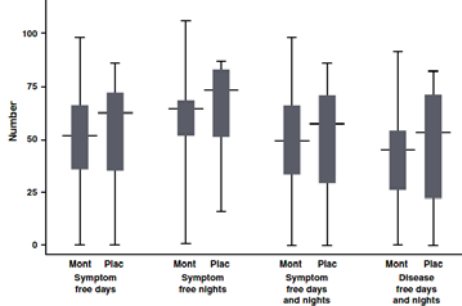
Primary outcome: the number of symptom-free days and disease-free days.

	Montelukast	Placebo	p-value
BPD y/n	1/30	0/27	1.00
Breastfeeding y/n	12/17	10/15	0.92
Eczema y/n	4/19	1/22	0.35
Daycare attendance y/n	10/18	10/16	0.84
Pets in the house y/n	12/18	9/16	0.76
Smoking parents y/n	7/23	1/24	0.59
Familial atopy y/n	14/16	9/17	0.36
Siblings y/n	5/20	10/20	0.37
Wheeze on admission	17/31	17/27	0.61
Ventilated y/n	1/30	1/27	1.00
nCPAP y/n	1/30	1/27	1.00
Age on admission (months)	3.5 (1.0-7.0)	3.3 (1.0-8.0)	0.75
Duration of admission (days)	6.0 (4.0-8.0)	5.5 (4.0-8.0)	0.41
Nights on oxygen (n)	0.5 (0.0-2.0)	1.0 (0.0-2.75)	0.70
PMA at birth (weeks)	39.0 (37-40)	39.5 (36-40)	0.63
Weight on admission (kg)	5.8 (4.5-7.2)	6.1 (4.5-8.0)	0.97
Length on admission (cm)	62.0 (53.0-70.0)	60.8 (53.8-73.2)	1.00

Proesmans M, et al. Montelukast does not prevent reactive airway disease in young children hospitalized for RSV bronchiolitis. *Acta Paediatr* 2009; 98: 1830-1834.

CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?

Symptom scores during the first 100 days after inclusion (14 weeks)



Proesmans M, et al. Montelukast does not prevent reactive airway disease in young children hospitalized for RSV bronchiolitis. *Acta Paediatr* 2009; 98: 1830-1834.

CQ1-2: Does motelukast prevent recurrent wheeze after RSV infection?

Number of exacerbations:

montelukast 41 (median of 1 per patient [quartiles 0-3])
 placebo 54 (median of 2 per patient [quartiles 0-3] (p = 0.57)
 during the 1 year follow-up

Median time [quartiles] interval to the first exacerbation

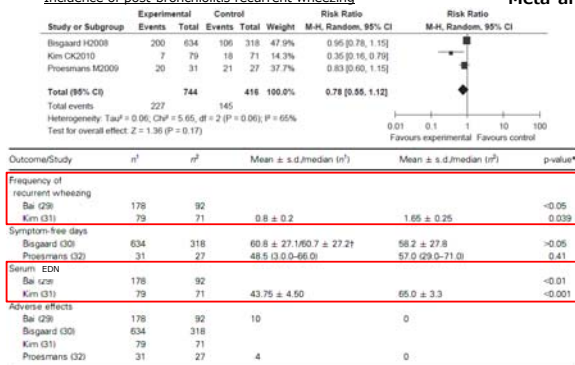
montelukast 25 days [0-77]
 placebo 6 days [0-58] for (p = 0.17)

Proesmans M, et al. Montelukast does not prevent reactive airway disease in young children hospitalized for RSV bronchiolitis. *Acta Paediatr* 2009; 98: 1830-1834.

CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?

Incidence of post-bronchiolitis recurrent wheezing

Meta-analysis



Peng WS, Systematic review of montelukast's efficacy for preventing post-bronchiolitis wheezing. *Pediatr Allergy Immunol* 2014; 25: 143-150.

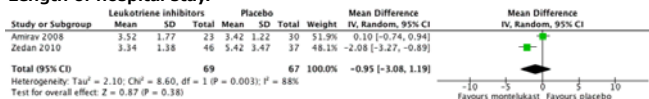
CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?

- Montelukast may reduce the frequency of post-bronchiolitic wheezing without causing significant side effects but that it has no effects on decreasing incidences of recurrent wheezing, symptom-free days, or the associated usage of corticosteroid in post-bronchiolitis patients.
- The small number of enrolled participants and the inability to pool all clinical outcomes precludes us from making solid recommendations.
- Subgroups that respond well to montelukast may exist. Eosinophil activation or elevated EDN may be a marker.

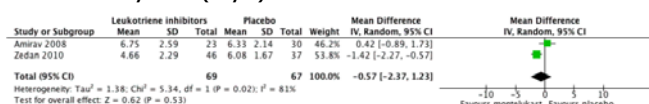
Peng WS, *Pediatr Allergy Immunol* 2014; 25: 143-150.

Leukotriene inhibitors may not be effective for acute symptoms of bronchiolitis

Length of hospital stay.



Clinical severity score (day 2)



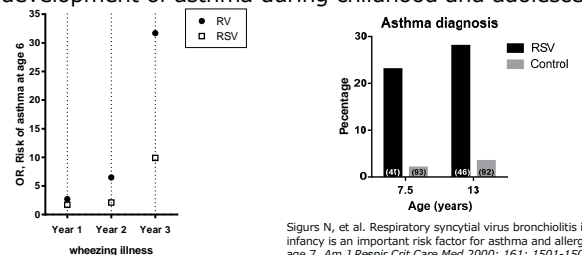
The current evidence does not allow definitive conclusions to be made about the effects of leukotriene inhibitors on length of hospital stay and clinical severity score in infants and young children with bronchiolitis.

Liu F, et al. Leukotriene inhibitors for bronchiolitis in infants and young children. *Cochrane Database Syst Rev* 2015; 3: CD010636.

CQ2: Does asthma medication prevent the development of asthma after RSV infection?

Background

- Associations between viral bronchiolitis and the development of asthma during childhood and adolescence



Sigurs N, et al. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000; 161: 1501-1507.

Jackson, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med*. 178:667-672. 2008.

Sigurs N, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005; 171: 137-141.

CQ2: Does asthma medication prevent the development of asthma after RSV infection?

- ICS

CQ2-1: Does ICS prevent the development of asthma after RSV infection?

Patients: 243 previously healthy infants (126 boys, 117 girls) aged less than 13 months and admitted to hospital with respiratory syncytial virus infection.

Interventions: **200 µg BDP (HFA)** twice daily or matched **placebo** administered by a pressurised metered dose inhaler and a spacer **during the first 3 months after hospital admission.**

Primary outcome: lung function, proportion of atopic diseases and height at 6 years of age

	Beclomethasone (n = 66)			Placebo (n = 69)		
	n	Absolute	% Predicted	n	Absolute	% Predicted
FEV ₁ (l)	66	1.21 (0.19)	91.4 (12.1)	69	1.26 (0.22)	93.4 (12.1)
FVC (l)	66	1.33 (0.22)	96.8 (13.7)	69	1.37 (0.26)	97.9 (13.7)
FEV ₁ /FVC (%)	66	91.6 (8.0)	96.7 (8.6)	69	92.4 (8.3)	97.5 (8.6)
PEF (L/s)	55	2.72 (0.38)	94.3 (17.1)	61	2.91 (0.56)	98.2 (17.1)
R _s (kPa L/s)	54	0.76 (0.23)	124.2 (37.2)	53	0.77 (0.25)	126.5 (36.2)
FcNO (ppb), median (IQR)	44	8.5 (6.0–12.0)	—	45	10.0 (6.0–14.9)	—
BHR present (n, %)	52	13 (25.0)	—	49	17 (34.7)	—

Zomer-Kooijker K, et al. Lack of long-term effects of high-dose inhaled beclomethasone for respiratory syncytial virus bronchiolitis: a randomized placebo-controlled trial. *Pediatr Infect Dis J* 2014; 33: 19-23.

CQ2-1: Does ICS prevent the development of asthma after RSV infection?

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Primary outcome: lung function, proportion of atopic diseases and height at 6 years of age

No difference

	Beclomethasone (n = 66)	Placebo (n = 69)
Asthma		
Physician-diagnosed asthma	21 (24.4)	21 (21.2)
Current asthma symptoms	36 (41.9)	41 (41.4)
Current medication use		
Inhaled steroids	5 (5.8)	9 (9.1)
Bronchodilator	10 (11.6)	9 (9.1)
Parent reported allergic diseases		
Asthma ever	8 (9.3)	14 (14.1)
Hayfever ever	7 (8.1)	6 (6.1)
Eczema ever	26 (30.2)	33 (33.3)

Zomer-Kooijker K, et al. Lack of long-term effects of high-dose inhaled beclomethasone for respiratory syncytial virus bronchiolitis: a randomized placebo-controlled trial. *Pediatr Infect Dis J* 2014; 33: 19-23.

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Primary outcome: lung function, proportion of atopic diseases and height at 6 years of age

Early initiated prolonged treatment with high-dose inhaled beclomethasone during hospitalization for respiratory syncytial virus infection during infancy **did not improve the long-term respiratory outcome**, but was safe.

	Beclomethasone (n = 66)	Placebo (n = 69)
Parent reported allergic diseases		
Asthma ever	8 (9.3)	14 (14.1)
Hayfever ever	7 (8.1)	6 (6.1)
Eczema ever	26 (30.2)	33 (33.3)

Zomer-Kooijker K, et al. Lack of long-term effects of high-dose inhaled beclomethasone for respiratory syncytial virus bronchiolitis: a randomized placebo-controlled trial. *Pediatr Infect Dis J* 2014; 33: 19-23.

CQ2: Does asthma medication prevent the development of asthma after RSV infection?

- Leukotriene receptor antagonist (LTRA)



No study has been reported

CQ3: Is asthma medication effective for preschool children with recurrent wheeze?

- ICS

CQ3-1: Is ICS effective for preschool children with recurrent wheeze?

A Systematic Review

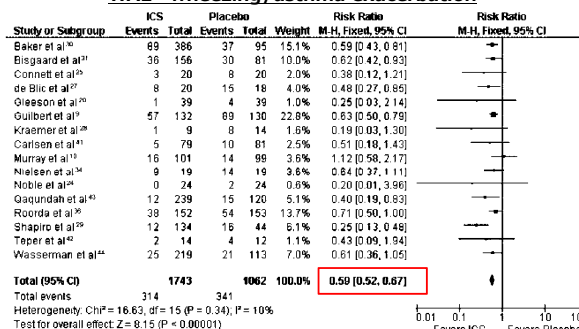
Inclusion criteria for trials

- (1) **infants (1–23 months old) or preschoolers (2–5 years old)** with a **clinical diagnosis of wheezing or asthma** for at least 6 months before study entry,
- (2) randomized (parallel group or crossover) controlled trials
- (3) a minimum of 4 weeks of treatment with ICSs (delivered via metered-dose inhaler [MDI] or nebulizer) compared with placebo
- (4) **primary outcome** measure of wheezing/asthma exacerbations (WAEs), define as worsening symptoms that required systemic corticosteroid use

Castro-Rodríguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics* 2009; 123: e519-525.

CQ3-1: Is ICS effective for preschool children with recurrent wheeze?

WAE—wheezing/asthma exacerbation



Castro-Rodríguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics* 2009; 123: e519-525.

CQ3: Is asthma medication effective for preschool children with recurrent wheeze?

- Leukotriene inhibitors

CQ3-2: Is montelukast effective for preschool children with recurrent wheeze?

Patients: 549 children aged 2 to 5 years with a history of intermittent asthma symptoms.

Interventions: **montelukast** (n=278) or **placebo** (n=271) once per day for **12 months**.

Primary outcome: the number of **asthma exacerbation** episodes defined as any **three consecutive days with daytime symptoms** (average score of four daily daytime symptom questions of at least 1.0 on each day) and **at least two treatments of beta-agonist per day, or rescue use of oral/inhaled corticosteroids during 1 or more days, or a hospitalization because of asthma**

Characteristic	Montelukast (n = 278)	Placebo (n = 271)
Sex, n (%)		
Male	173 (62)	177 (65)
Female	105 (38)	94 (35)
Race, n (%)		
White	188 (68)	184 (68)
Asian	47 (17)	39 (14)
Black	2 (0.7)	1 (0.4)
Hispanic	40 (14)	43 (16)
Other	1 (0.4)	4 (1.5)
Age categories, n (%)		
< 36 mo	85 (31)	79 (29)
36-47 mo	94 (34)	93 (35)
48-59 mo	46 (17)	49 (18)
≥ 60 mo	51 (18)	44 (16)
Age, median (range), mo	44 (24-72)	44 (24-72)

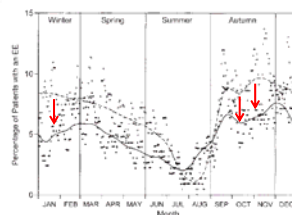
Bisgaard H, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005; 171: 315-322.

Characteristic	Montelukast (n = 278)	Placebo (n = 271)
Daytime asthma symptom score ^a	n ^b = 276	n ^b = 269
median (range)	0.0 (0.0-0.7)	0.0 (0.0-0.9)
B-agonist use ^c , puffs/14 d	n ^b = 261	n ^b = 255
median (range)	0 (0-36)	0 (0-28)
Oral corticosteroid use for worsening asthma ^d , n (%)	n ^b = 277	n ^b = 271
≤ 2 courses	247 (89)	257 (95)
> 3 courses	30 (11)	14 (5)
Frequency of asthma symptoms ^e , n (%)	n ^b = 278	n ^b = 270
≤ 2 times/wk	231 (83)	235 (87)
> 2 times/wk	47 (17)	35 (13)
Nocturnal awakenings ^f	n ^b = 278	n ^b = 271
≤ 2 times/mo	226 (81)	235 (87)
> 2 times/mo	52 (19)	36 (13)
Positive RAST test, n (%)	n ^b = 265	n ^b = 264
	90 (34%)	94 (36%)

Bisgaard H, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005; 171: 315-322.

CQ3-2: Is montelukast effective for preschool children with recurrent wheeze?

	Montelukast (n = 265)	Placebo (n = 257)	Montelukast vs. Placebo		
	Rate/yr ^a (95% CI)	Rate/yr ^a (95% CI)	Relative Rate (95% CI)	Rate Reduction ^b	p Value
Asthma exacerbation					
Episodes	1.60 (1.35, 1.88)	2.34 (1.97, 2.79)	0.68 (0.56, 0.83)	31.9%	≤ 0.001
Corticosteroid courses	1.19 (0.94, 1.51)	1.74 (1.39, 2.18)	0.68 (0.49, 0.95)	31.6%	0.024
Inhaled	0.66 (0.46, 0.94)	1.16 (0.83, 1.45)	0.60 (0.38, 0.94)	39.8%	0.027
Oral	0.53 (0.40, 0.70)	0.64 (0.47, 0.88)	0.82 (0.54, 1.25)	17.5%	0.368



Montelukast effectively reduced asthma exacerbations in 2- to 5-year-old patients with intermittent asthma over 12 months of treatment and was generally well tolerated.

Bisgaard H, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005; 171: 315-322.

CQ4: Is intermittent asthma medication effective for recurrent wheeze/asthma?

- ICS
- Leukotriene receptor antagonist (LTRA)

CQ4-1: Is intermittent asthma medication effective for recurrent wheeze/asthma?

Patients: 238 children aged 12 to 59 months with moderate-to severe intermittent wheezing.
Interventions: 7 days of either **budesonide inhalation suspension** (1 mg twice daily), **montelukast**, or **placebo** in addition to albuterol **with each identified respiratory tract illness (RTI)** during the **12-month trial**
Primary outcome: Proportion of **episode-free days (EFDs)**

	Montelukast (n = 95)	Budesonide (n = 96)	Conventional therapy (n = 47)
Demographics/asthma history			
Age (mo)	35.4 ± 12.4	36.7 ± 13.5	35.7 ± 13.7
Male sex (%)†	65.3	72.9	48.9
Minority (%)	23.2	25.9	25.5
Height (cm)	95.2 ± 8.0	95.2 ± 9.6	94.4 ± 10.2
Age at doctor's diagnosis of asthma (y)†	1.4 ± 0.9 (n = 56)	1.6 ± 1.1 (n = 62)	1.5 ± 1.1 (n = 31)
Age of onset of asthma (y)†	1.0 ± 0.8 (n = 56)	1.1 ± 1.0 (n = 62)	1.0 ± 0.9 (n = 30)
ED visits for wheezing in past year			
No. per year	1.1 ± 2.9	0.9 ± 1.4	1.1 ± 1.5
Percentage of participants	36.8	40.6	46.8
Doctor's visits for wheezing in past year			
No. per year	4.3 ± 3.4	3.7 ± 2.5	4.7 ± 3.4
Percentage of participants	9.5	5.2	10.6
Missed school/day care days in past year			
	5.5 ± 12.4 (n = 58)	4.8 ± 6.2 (n = 65)	3.7 ± 5.6 (n = 34)
Exposed to tobacco smoke at home or day care (%)			
	4.2	4.2	1.7

Bacharier LB, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008; 122: 1127-1135.

CQ4-1: Is intermittent asthma medication effective for recurrent wheeze/asthma?

	Montelukast (n = 94)	Budesonide (n = 96)	Conventional therapy (n = 47)
Primary outcome			
Proportion of EFDs*	0.73 (0.66-0.79)	0.76 (0.70-0.81)	0.74 (0.65-0.81)
Secondary outcomes			
No. of RTIs/participant			
	3.4 (2.9-3.9)	3.7 (3.2-4.2)	3.6 (3.0-4.3)
Oral corticosteroid use			
Time to first oral corticosteroid course (d), median (lower quartile-upper quartile)			
	292 (85-364)	354 (137-365)	292 (127-359)
No. of oral corticosteroid courses/participant*			
	1.0 (0.7-1.3)	0.7 (0.5-1.0)	0.9 (0.6-1.4)
Percentage of participants receiving ≥1 course			
	46.8 (36.4-57.4)	38.5 (28.8-49.0)	55.3 (40.1-69.8)
Days of oral corticosteroid use/participant*			
	4.3 (3.7-5.8)	2.9 (2.1-4.1)	3.0 (1.9-4.8)
Health care use			
Percentage with ≥1 urgent care or ED visit			
	54.8 (44.7-65.6)	53.7 (43.7-64.4)	55.6 (40.1-69.8)
Hospitalization (%)			
	6.4 (2.4-13.4)	2.1 (0.25-7.3)	8.5 (2.4-20.4)
No. of urgent care and ED visits/participant*			
	1.5 (1.1-2.0)	1.1 (0.8-1.5)	1.6 (1.1-2.3)
Days missed from school or day care/participant (no. who attended school or day care)*			
	2.9 (2.0-4.3) (n = 61)	2.1 (1.4-3.1) (n = 69)	2.6 (1.7-4.1) (n = 35)
Quality of life			
PACQLQ total score (change)*†			
	-0.11 (-0.33-0.11)	-0.04 (-0.24-0.17)	-0.03 (-0.25-0.31)
PeDQLQ total score (change)*†			
	0.88 (-0.21 to 4.08)	0.49 (-3.07 to 4.04)	-2.79 (-7.02-1.45)
Growth (cm)			
	7.9 (7.4-8.3)	7.8 (7.4-8.1)	7.5 (7.0-8.1)

Bacharier LB, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008; 122: 1127-1135.

	Montelukast (n = 95)	Budesonide (n = 96)	Conventional therapy (n = 47)
Medication use in previous year			
Any controller (%)			
	36.8	36.5	27.7
ICS (%)			
	34.7	32.3	19.2
Leukotriene modifier (%)			
	6.3	7.3	8.5
Long-acting β-agonist (%)			
	1.1	0	0
No. of oral corticosteroid courses, no. (%)			
0 = 35 (36.8%)	0 = 39 (40.6%)	0 = 22 (46.8%)	
1 = 25 (26.3%)	1 = 21 (21.9%)	1 = 13 (27.7%)	
2 = 17 (17.9%)	2 = 25 (26.0%)	2 = 8 (17.0%)	
3 = 6 (6.3%)	3 = 8 (8.3%)	3 = 2 (4.3%)	
4+ = 12 (12.6%)	4+ = 3 (3.1%)	4+ = 2 (4.3%)	
Atopic characteristics			
Positive aeroallergen ST (%)			
	50.0	44.8	44.7
Positive aeroallergen ST (no.)			
	1.0 ± 1.3	0.8 ± 1.3	0.8 ± 1.1
IgE (IU/mL), geometric mean ± CV			
	35.4 ± 5.5	39.8 ± 4.5	47.5 ± 6.0
Eosinophils (%)			
	4.0 ± 2.7	4.4 ± 3.0	4.6 ± 3.4
Eczema (%)			
	28.4	34.4	42.6
Parental asthma (%)			
	41.6	41.7	53.2
API positive (%)			
	60.0	58.3	66.0
Quality of Life			
PACQLQ overall score†			
	6.6 ± 0.6	6.5 ± 0.9	6.5 ± 0.8
PeDQLQ total score score†			
	89.8 ± 8.8	88.3 ± 12.6	90.6 ± 7.9

Bacharier LB, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008; 122: 1127-1135.

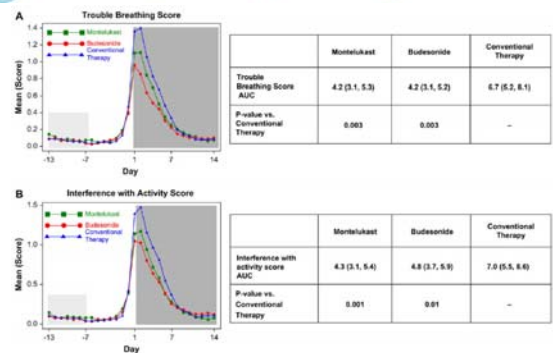
CQ4-1: Is intermittent asthma medication effective for recurrent wheeze/asthma?

	Montelukast (n = 94)	Budesonide (n = 96)	Conventional therapy (n = 47)
Primary outcome			
Proportion of EFDs*	0.73 (0.66-0.79)	0.76 (0.70-0.81)	0.74 (0.65-0.81)
Secondary outcomes			
No. of RTIs/participant			
	3.4 (2.9-3.9)	3.7 (3.2-4.2)	3.6 (3.0-4.3)
Oral corticosteroid use			
Time to first oral corticosteroid course (d), median (lower quartile-upper quartile)			
	292 (85-364)	354 (137-365)	292 (127-359)
No. of oral corticosteroid courses/participant*			
	1.0 (0.7-1.3)	0.7 (0.5-1.0)	0.9 (0.6-1.4)
Percentage of participants receiving ≥1 course			
	46.8 (36.4-57.4)	38.5 (28.8-49.0)	55.3 (40.1-69.8)
Days of oral corticosteroid use/participant*			
	4.3 (3.7-5.8)	2.9 (2.1-4.1)	3.0 (1.9-4.8)
Health care use			
Percentage with ≥1 urgent care or ED visit			
	54.8 (44.7-65.6)	53.7 (43.7-64.4)	55.6 (40.1-69.8)
Hospitalization (%)			
	6.4 (2.4-13.4)	2.1 (0.25-7.3)	8.5 (2.4-20.4)
No. of urgent care and ED visits/participant*			
	1.5 (1.1-2.0)	1.1 (0.8-1.5)	1.6 (1.1-2.3)
Days missed from school			
	2.9 (2.0-4.3) (n = 61)	2.1 (1.4-3.1) (n = 69)	2.6 (1.7-4.1) (n = 35)

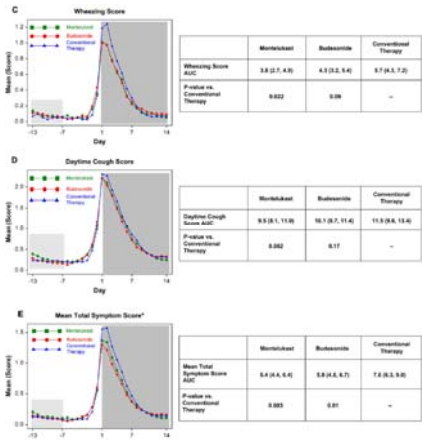
In preschool children with moderate-to-severe intermittent wheezing, episodic use of either budesonide or montelukast early in RTIs, when added to albuterol, did not increase the proportion of EFDs or decrease oral corticosteroid use over a 12-month period

Bacharier LB, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008; 122: 1127-1135.

CQ4-1: Is intermittent asthma medication effective for recurrent wheeze/asthma?



Bacharier LB, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008; 122: 1127-1135.



Budesonide or montelukast initiated at early signs of RTI significantly **reduced episode severity** relative to conventional therapy

Montelukast reduced... wheezing
trouble breathing
activity limitation
Budesonide reduced... trouble breathing
activity limitation

Bacharier LB, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008; 122: 1127-1135.

CQ4: Is intermittent asthma medication effective for recurrent wheeze/asthma?

- Leukotriene receptor antagonist (LTRA)

CQ4-2: Is intermittent montelukast effective for recurrent wheeze/asthma?

Patients: 1358 Children aged 10 months to 5 years with two or more wheeze
Interventions: intermittent **montelukast** or **placebo** given by parents at each wheeze episode over a 12 month period.
allocated to either a 5/5 or 5/x+x/x **ALOX5** promoter genotype stratum
Primary outcome: number of unscheduled medical attendances for wheezing episodes

	Montelukast group (n=669)			Placebo group (n=677)		
	5/5	5/x+x/x	Total	5/5	5/x+x/x	Total
n (%)	416 (62%)	253 (38%)	669 (100%)	426 (63%)	251 (37%)	677 (100%)
Height (cm)	90.0 (10.3)	89.8 (10.5)	89.9 (10.4)	89.9 (10.5)	91.8 (11.7)	90.6 (11.0)
Weight (kg)	14.0 (3.0)	13.9 (3.7)	14.0 (3.3)	14.0 (3.3)	14.6 (3.8)	14.2 (3.5)
Age (years)	2.6 (1.1)	2.5 (1.1)	2.6 (1.1)	2.6 (1.1)	2.8 (1.2)	2.7 (1.1)
Male sex	262 (63%)	164 (65%)	426 (64%)	276 (65%)	161 (64%)	437 (65%)
Ethnic origin						
White	335 (81%)	179 (71%)	514 (77%)	338 (79%)	174 (69%)	512 (76%)
Black	5 (1%)	14 (6%)	19 (3%)	4 (1%)	14 (6%)	18 (3%)
Asian	55 (13%)	37 (15%)	92 (14%)	58 (14%)	46 (18%)	104 (15%)
Other	21 (5%)	23 (9%)	44 (7%)	26 (6%)	17 (7%)	43 (6%)
Premature birth (<37 weeks)	58 (14%)	40 (16%)	98 (14%)	56 (13%)	42 (17%)	98 (15%)
Birthweight (<2500g)	51 (12%)	28 (11%)	79 (12%)	42 (10%)	28 (11%)	70 (10%)

Nwokoro et al. Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): a multicentre, randomised, placebo-controlled trial. *Lancet Respir Med* 2014; 2: 796-803.

	Montelukast group (n=669)			Placebo group (n=677)		
	5/5	5/x+x/x	Total	5/5	5/x+x/x	Total
Food allergy	64 (15%)	44 (18%)	108 (16%)	64 (15%)	47 (18%)	111 (17%)
Drug allergy	26 (6%)	12 (5%)	38 (6%)	23 (6%)	19 (8%)	42 (6%)
Itchy rash (>5 months, ever)*	98 (23%)	64 (25%)	162 (24%)	104 (25%)	60 (24%)	164 (25%)
Eczema (ever)†	207 (49%)	121 (48%)	328 (48%)	215 (52%)	134 (53%)	349 (52%)
History of asthma in mother	156 (37%)	95 (38%)	251 (37%)	141 (34%)	89 (35%)	230 (34%)
History of asthma in father	126 (30%)	73 (29%)	199 (29%)	126 (30%)	81 (32%)	207 (31%)
Age at first wheeze (months)	12.4 (9.8)	13.5 (10.5)	12.8 (10.1)	12.4 (10.4)	13.6 (11.5)	12.9 (10.8)
Children with episodic oral wheeze	296 (71%)	181 (72%)	477 (71%)	295 (69%)	191 (76%)	486 (72%)
Children with multitrigger wheeze	120 (29%)	72 (28%)	192 (29%)	131 (31%)	60 (24%)	191 (28%)
Interval between onset of URTI and wheezing (h)‡	31.6 (27.4)	28.8 (25.2)	30.5 (26.4)	27.3 (23.4)	28.2 (26.0)	27.7 (24.4)
Children with more than one hospital admission for wheeze in the past year	363 (87%)	216 (85%)	579 (87%)	351 (82%)	203 (81%)	554 (82%)
Courses of oral corticosteroids in past year	2.0 (1.9)	1.8 (1.8)	1.9 (1.8)	1.9 (1.9)	1.8 (2.0)	1.9 (2.0)
USMA in previous year	55 (13%)	54 (21%)	109 (16%)	57 (13%)	56 (22%)	113 (17%)
Continuous inhaled corticosteroids	118 (28%)	66 (26%)	184 (28%)	144 (34%)	69 (27%)	213 (31%)

Nwokoro et al. Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): a multicentre, randomised, placebo-controlled trial. *Lancet Respir Med* 2014; 2: 796-803.

CQ4-2: Is intermittent montelukast effective for recurrent wheeze/asthma?

Treatment response in the primary analysis, and by 5/5 and 5/x+x/x strata

	Montelukast group (n=652)	Placebo group (n=656)	Adjusted incidence rate ratio (95% CI)	p value	P _{interaction}
Primary analysis					
USMA episodes	2.0 (2.6)	2.3 (2.7)	0.88 (0.77-1.01)	0.06	..
Subgroup analysis					
USMA in 5/5 stratum	2.0 (2.7)	2.4 (3.0)	0.80 (0.68-0.95)	0.01	..
USMA in 5/x+x/x stratum	2.0 (2.5)	2.0 (2.3)	1.03 (0.83-1.29)	0.79	0.08

No clear benefit of intermittent montelukast in young children with wheeze. However, the 5/5 ALOX5 promoter genotype might identify a montelukast-responsive subgroup

Nwokoro et al. Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): a multicentre, randomised, placebo-controlled trial. *Lancet Respir Med* 2014; 2: 796-803.

CQ4: Is intermittent asthma medication effective for recurrent wheeze/asthma?

- ICS; intermittent versus daily

CQ4-3: Is intermittent ICS effective for recurrent wheeze/asthma?

Patients: 278 children between the ages of 12 and 53 months who had positive values on the modified API, recurrent wheezing episodes, and at least one exacerbation in the previous year but a low degree of impairment.

Interventions: randomly assigned to receive a **budesonide inhalation suspension for 1 year** as either an **intermittent high-dose regimen (1 mg twice daily for 7 days, starting early during a predefined respiratory tract illness)** or a **daily low-dose regimen (0.5 mg nightly)** with **corresponding placebos**

Primary outcome: **frequency of exacerbations** requiring oral glucocorticoid therapy

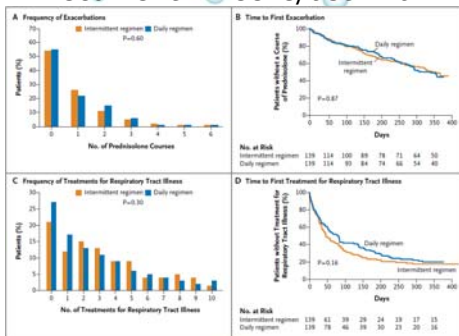
Table 1. Demographic and Asthma Characteristics of the Patients.*

Characteristic	Total (N=278)	Intermittent Regimen (N=139)	Daily Regimen (N=139)
Age of 12–32 mo — no. (%)	127 (45.7)	64 (46.0)	63 (45.3)
Male sex — no. (%)	192 (69.1)	102 (73.4)	90 (64.7)
White race — no. (%)†	173 (62.2)	91 (65.5)	82 (59.0)
Height — cm	94.2±9.1	94.0±9.1	94.5±9.0
Weight — kg	15.2±3.1	15.0±3.0	15.5±3.1
Head circumference — cm	50.0±1.9	50.1±2.0	49.9±1.9

Zeiger RS, et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med* 2011; 365: 1990-2001.

Characteristic	Total (N=278)	Intermittent Regimen (N=139)	Daily Regimen (N=139)
Physician diagnosis of asthma — no. (%)	188 (77.2)	99 (77.2)	89 (77.2)
No. of wheezing episodes in past year	6.7±5.4	7.0±5.9	6.4±4.7
No. of urgent or emergency visits in past year	4.8±4.2	4.6±4.2	5.0±4.1
Hospitalizations in past year — no. (%)	53 (19.1)	28 (18.7)	27 (19.4)
Tobacco-smoke exposure from birth — no. (%)	114 (41.0)	55 (39.6)	59 (42.4)
Medication use in past year — no. (%)			
Asthma controller	194 (69.8)	100 (71.9)	94 (67.6)
Inhaled glucocorticoid	189 (68.0)	96 (69.1)	93 (66.9)
Oral glucocorticoid	210 (75.5)	110 (79.1)	100 (71.9)
Allergy — no./total no. (%)			
Food sensitivity	95/273 (34.8)	50/135 (37.0)	45/138 (32.4)
Any aeroallergen sensitivity	161/276 (58.3)	82/137 (59.9)	79/139 (56.8)
IgE — IU/ml			
Median	58	50	61
Interquartile range	21–186	20–195	25–179
Eosinophils ≥4% — no./total no. (%)	123/260 (47.3)	61/132 (46.2)	62/128 (48.4)
Eczema — no. (%)	146 (52.5)	72 (54.7)	70 (50.4)
Allergic rhinitis — no. (%)	103 (37.8)	50 (36.0)	53 (39.4)
Parental asthma — no./total no. (%)	171/268 (64.3)	85/131 (64.9)	86/135 (63.7)
Exhaled nitric oxide ≥10 ppb — no./total no. (%)	78/178 (43.8)	36/82 (43.9)	42/96 (43.8)
Episode-free days during run-in period — %	67±30	66±30	68±29
Diary scores during run-in period:			
Coughing	0.4±0.4	0.4±0.5	0.4±0.4
Wheezing	0.1±0.3	0.2±0.3	0.1±0.3
Trouble breathing	0.1±0.3	0.1±0.3	0.1±0.2
Interference with activities	0.1±0.2	0.1±0.2	0.1±0.3
General health perceptions from ITQOL§	59.2±14.1	59.0±14.8	59.4±13.5
Any nasal virus identified — no. (%)	148 (53.2)	72 (51.8)	76 (54.7)

CQ4-3: Is intermittent ICS effective for recurrent wheeze/asthma?



The daily regimen of budesonide did not differ significantly from the intermittent regimen with respect to the frequency of exacerbations

Zeiger RS, et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med* 2011; 365: 1990-2001.

Summary

- Diagnosis is the key...
 - whether a young child with recurrent wheeze needs asthma controllers?
- Prevention
 - Post-RSV: Montelukast may be effective?, not ICS
- Long-term control
 - ICS is the mainstay, montelukast is also effective
 - Intermittent use...still to be studied
 - Genotype or endotype-specific treatment?