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New Asthma Guidelines: Special Attention to Infant Wheezers

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EPR 3: Current Status

- The initial version of the EPR 3 was a draft document and was open for public review from February 5 until March 5, 2007.
- It was revised following analysis of comments collected during the public review.
- An official full report as a Resource Document was posted on August 29, 2007:

http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

- An Executive Summary was published in November 2007 – NIH web site and JACI.

EPR 3: Primary Themes

- Comprehensive, systematic review of the scientific evidence for the treatment of asthma
- Treatment recommendations based on the concepts of
  - Severity
  - Control

  } Includes the domains of *current impairment* and *future risk*
  - Responsiveness
- EPR 3 provides standardized definitions of these important concepts

NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3). Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed August 31, 2007.

Severity, Control, and Responsiveness

- Severity
  - Intrinsic intensity of the disease process
  - Most easily and directly measured in patients not receiving long-term therapy
- Control
  - Degree to which asthma-related symptoms, functional impairment, and risk of untoward events are minimized and goals of therapy are met
- Responsiveness
  - Ease with which asthma control is achieved by therapy
  - Highly variable to asthma treatment

NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3). Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed August 31, 2007.

Current Impairment and Future Risk

- Both severity and control include the domains of *current impairment and future risk*
- Impairment
  - Frequency and intensity of symptoms and functional limitations the patient is currently or has recently experienced
- Risk
  - Likelihood of asthma exacerbations, progressive decline in lung function, or risk of adverse effects from medications

NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3). Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed August 31, 2007.

Summary

- EPR 3 refines the concepts of asthma severity, control, and responsiveness to treatment
  - Defines severity and control in terms of impairment and risk
  - Periodic assessment of severity and control guide asthma management
- Goal of treatment is to achieve and maintain control by reducing current impairment and long-term risk
- Long-term control medications with anti-inflammatory actions recommended for use on a daily basis with defined treatment steps for three distinct age groups.

NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3). Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed August 31, 2007.

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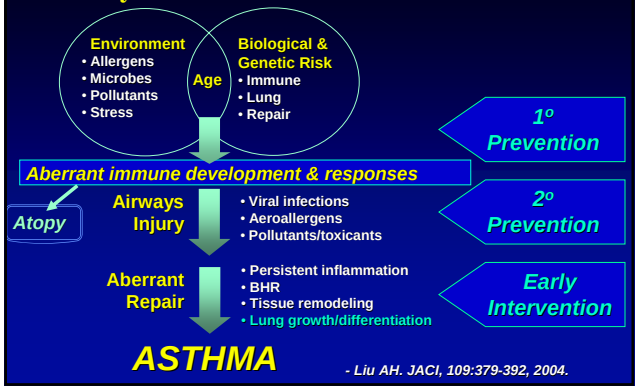
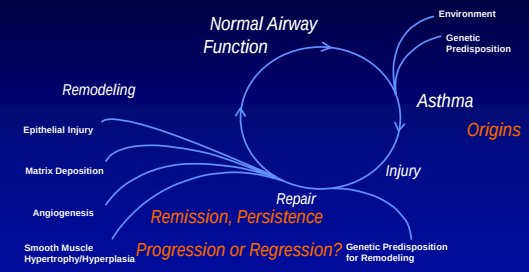
Early Intervention for Asthma Prevention



- Liu AH. JACI, 109:379-392, 2004.

Asthma Pathways



Lazaar AL, Panettieri R. Am J Med. 2003;115:652-659.

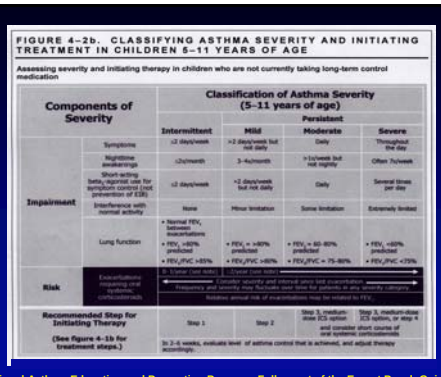
Asthma in Children Starts Early

McNicol and Williams. *Br Med J* 1973;4:7-11.
Wainwright et al. *Med J Aust* 1997;167:218-222.

Improving Asthma Control

Goals of long-term control therapy

- Prevent symptoms
- Improve pulmonary function
- Reduce inflammation
- Resolve and prevent progression



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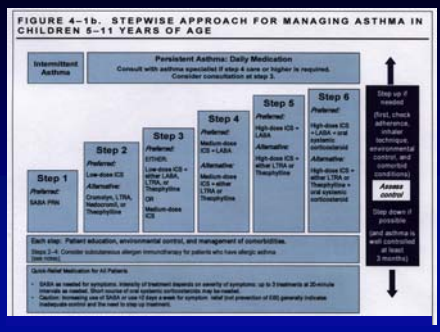

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FIGURE 4–3b. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 5–11 YEARS OF AGE

Components of Control		Classification of Asthma Control (5–11 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week but not more than once on each day	>2 days/week or multiple times on ≤2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	>2x/month	≥2x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Lung function			
	• FEV_1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	• FEV_1/FVC	>85%	75–80%	<75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Reduction in lung growth	Evaluation requires long-term follow-up.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (See figure 4–1b for treatment steps.)		• Maintain current step. • Regular follow-up every 1–6 months. • Consider step down if well controlled for at least 3 months.	• Step up at least 1 step and • Reevaluate in 2–6 weeks. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids. • Step up 1–2 steps, and • Reevaluate in 2 weeks. • For side effects, consider alternative treatment options.

NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3). Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed August 31, 2007.

BOX 4–1. SAMPLE RECORD FOR MONITORING THE RISK DOMAIN IN CHILDREN: RISK OF ASTHMA PROGRESSION (INCREASED EXACERBATIONS OR NEED FOR DAILY MEDICATION, OR LOSS OF LUNG FUNCTION), AND POTENTIAL ADVERSE EFFECTS OF CORTICOSTEROID THERAPY

Patient name:					
Date					
Long-term control medication					
ICS daily dose*					
LTRA					
LABA					
Theophylline					
Other					
Significant exacerbations					
Exacerbations (number/month)					
Oral systemic corticosteroids (number/year)*					
Hospitalization (number/year)					
Pulmonary function					
Prebronchodilator FEV_1/FVC					
Prebronchodilator FEV_1 percent predicted					
Postbronchodilator FEV_1 percent predicted					
Percent bronchodilator reversibility					
Potential risk of adverse corticosteroid effects (as indicated by corticosteroid dose and duration of treatment)					
Height, cm					
Percentile					
Plots of growth velocity					

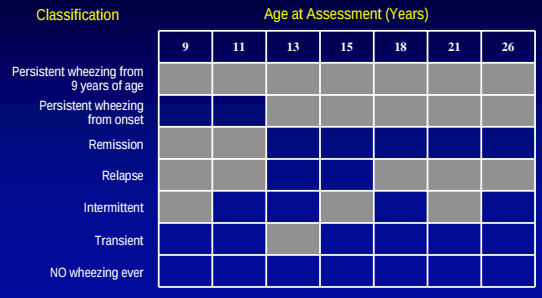
FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist
*Consider ophthalmologic exam and bone density measurement in children using high doses of ICS or multiple courses of oral corticosteroids.

NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3). Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed August 31, 2007.

Potential Approaches to Improving Asthma Control

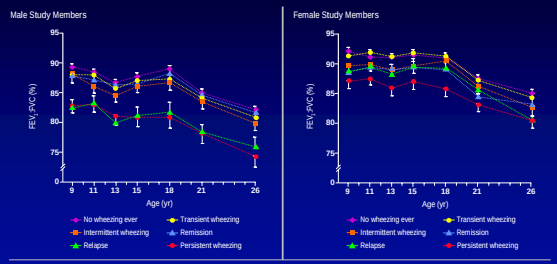
- Early intervention
- Combination therapy
- Biomarkers
- Genetics
- Immunomodulators

The "Natural History" Asthma Phenotype



Sears MR, et al. N Engl J Med. 2003;349:1414-1422.

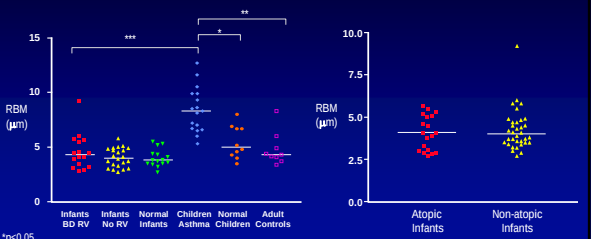
Outcomes in Pulmonary Function Based on "Natural History" Asthma Phenotype



Mean (±SE) FEV_1:FVC ratios measured at 9, 11, 13, 15, 18, 21, and 26 years in male and female study members, according to the pattern of wheezing.

Sears MR, et al. N Engl J Med. 2003;349:1414-1422.

Airway Remodeling & Inflammation *RBM Thickness in Infants*



*p<0.05
**p<0.01
***p<0.001
RBM, reticular basement membrane; RV, reversibility
Saglani S, et al. Am J Respir Crit Care Med. 2005;171:722-727.

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Key Recommendations

Managing asthma in children 0 - 4 years

- Diagnosis is <u>often difficult</u>.
- Treatment has <u>not been adequately studied</u>.
- Criteria for <u>initiation</u> of long-term control therapy:
  - 3 wheezing episodes in past year and positive <u>asthma risk profile</u>.
  - those who require <u>symptomatic treatment</u> > 2 days per week
  - two or more <u>severe exacerbations</u> within 6 months

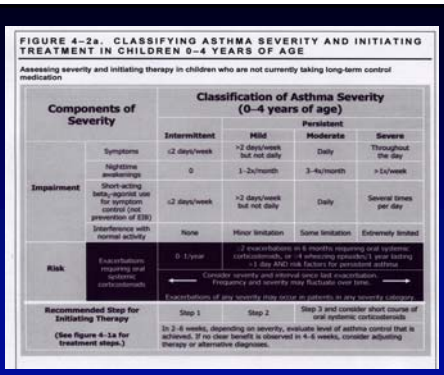
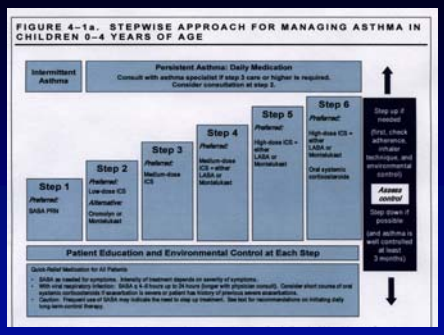


FIGURE 4–2a. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 0–4 YEARS OF AGE

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of Severity		Classification of Asthma Severity (0–4 years of age)			
		Intermittent	Persistent: Mild	Persistent: Moderate	Persistent: Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2x/month	3–4x/month	>1x/week
	Short-acting beta2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or >4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time.			
		Exacerbations of any severity may occur in patients in any severity category.			
Recommended Step for Initiating Therapy (See figure 4–1a for treatment steps.)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	
		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.			

NHLBI. National Asthma Education and Prevention Program. Full report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3). Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed August 31, 2007.



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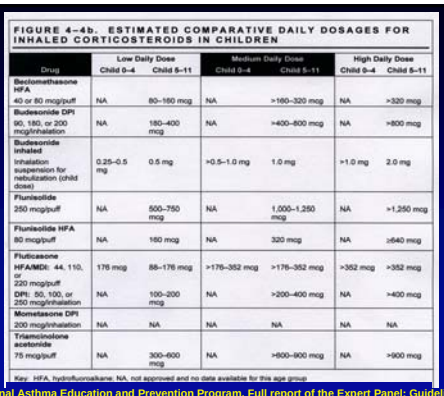

FIGURE 4–4b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS IN CHILDREN

Drug	Low Daily Dose: Child 0–4	Low Daily Dose: Child 5–11	Medium Daily Dose: Child 0–4	Medium Daily Dose: Child 5–11	High Daily Dose: Child 0–4	High Daily Dose: Child 5–11
Beclomethasone HFA 40 or 80 mcg/puff	NA	80–160 mcg	NA	>160–320 mcg	NA	>320 mcg
Budesonide DPI 90, 180, or 200 mcg/inhalation	NA	180–400 mcg	NA	>400–800 mcg	NA	>800 mcg
Budesonide inhaled inhalation suspension for nebulization (child dose)	0.25–0.5 mg	0.5 mg	>0.5–1.0 mg	1.0 mg	>1.0 mg	2.0 mg
Flunisolide 250 mcg/puff	NA	500–750 mcg	NA	1,000–1,250 mcg	NA	>1,250 mcg
Flunisolide HFA 80 mcg/puff	NA	160 mcg	NA	320 mcg	NA	≥640 mcg
Fluticasone HFA/MDI: 44, 110, or 220 mcg/puff	176 mcg	88–176 mcg	>176–352 mcg	>176–352 mcg	>352 mcg	>352 mcg
DPI: 50, 100, or 250 mcg/inhalation	NA	100–200 mcg	NA	>200–400 mcg	NA	>400 mcg
Mometasone DPI 200 mcg/inhalation	NA	NA	NA	NA	NA	NA
Triamcinolone acetonide 75 mcg/puff	NA	300–600 mcg	NA	>600–900 mcg	NA	>900 mcg

Key: HFA, hydrofluoroalkane; NA, not approved and no data available for this age group

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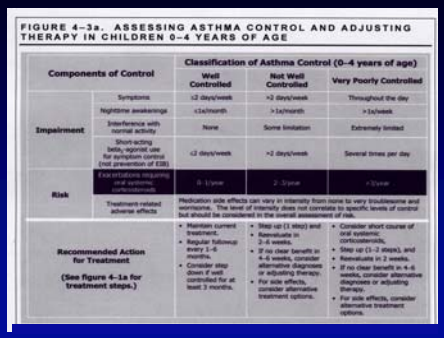

FIGURE 4–3a. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 0–4 YEARS OF AGE

Components of Control		Classification of Asthma Control (0–4 years of age): Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	>1x/month	>1x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	2–3/year	>3/year
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (See figure 4–1a for treatment steps.)		• Maintain current treatment. • Regular follow-up every 1–6 months. • Consider step down if well controlled for at least 3 months.	• Step up (1 step) and reevaluate in 2–6 weeks. • If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids. • Step up (1–2 steps), and • Reevaluate in 2 weeks. • If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy. • For side effects, consider alternative treatment options.

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Childhood Asthma Management Program

- Clinical measures of control strongly favored Budesonide over Placebo
  - Symptoms
  - Rescue medication use and prednisone courses
  - Episode-free days
  - Hospitalizations and urgent care
  - Initiation of beclomethasone or additional asthma medication

CAMP, NEJM 343(15) 2000

CAMP

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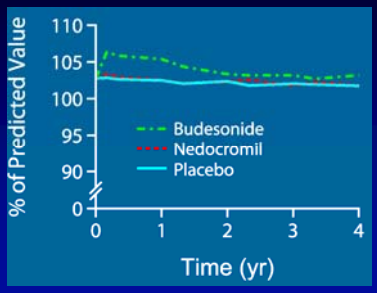
FEV_1 After Bronchodilator



CAMP, NEJM 343(15) 2000

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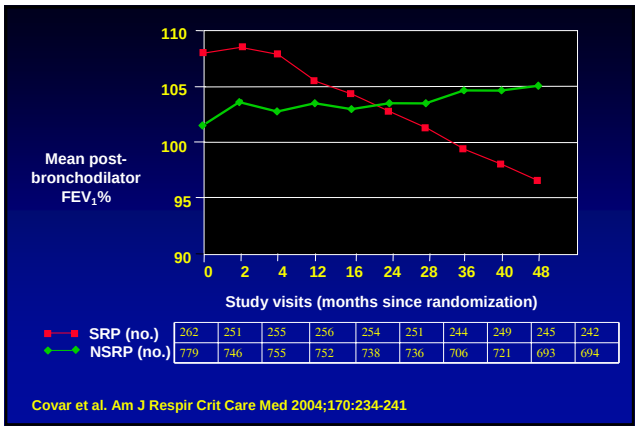
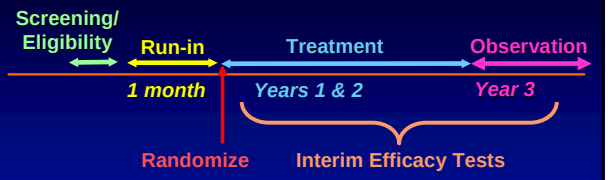


Covar et al. Am J Respir Crit Care Med 2004;170:234-241

PEAK: Study Design



- **Randomized, multicenter, double-blind, parallel group, placebo-controlled trial**
- **285 two and three year olds at high-risk for asthma**
- **Fluticasone 44 µg/puff or placebo (2 puffs b.i.d.)**

Asthma Predictive Index

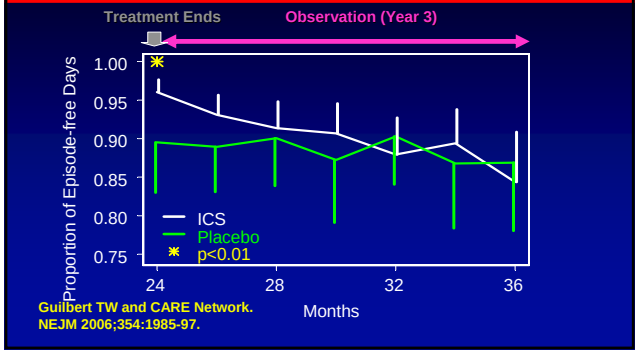
- Identify high risk children (ages 2 & 3):
  - ≥ 4 wheezing episodes in the past year (at least one must be MD diagnosed)
  PLUS
  - One major criteria *OR* - Two minor criteria
    - Parent with asthma
    - Atopic dermatitis
    - Aero-allergen sensitivity
    - Food sensitivity
    - Peripheral eosinophilia (≥4%)
    - Wheezing not related to infection

Modified from: Castro-Rodriguez, AJRRCM, 2000

PEAK: Primary Outcome

- *Episode-free days during the observation-year*
  - No cough or wheeze
  - No unscheduled clinic, urgent care, ER or hospital visits
  - No use of asthma medications including bronchodilator pre-treatment before exercise

Episode-free Days During Observation Year



Guilbert TW and CARE Network. NEJM 2006;354:1985-97.

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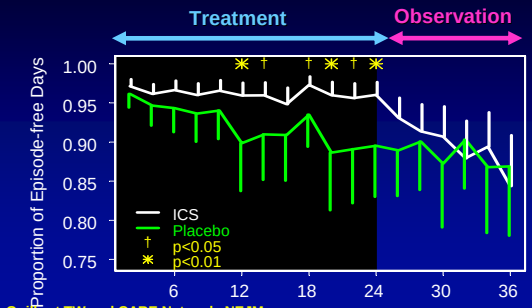
Outcomes During Observation Phase

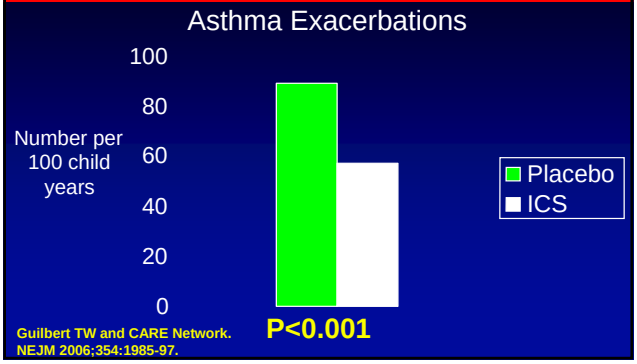
- No differences between groups seen for:
  - Number of exacerbations requiring systemic corticosteroid bursts
  - Unscheduled physician visits
  - Hospitalizations
  - Bronchodilator use
  - Montelukast use
  - Respiratory system impedance
- Average # of days of supplemental ICS use: 26% less in ICS group (p=0.007) during first 3 months
- There were no significant differences in adherence, completed visits, drop-outs, treatment failures or serious adverse events between study groups.

Episode-free Days During the Entire Study



Guilbert TW and CARE Network. NEJM 2006;354:1985-97.

ICS Effect During Treatment Phase



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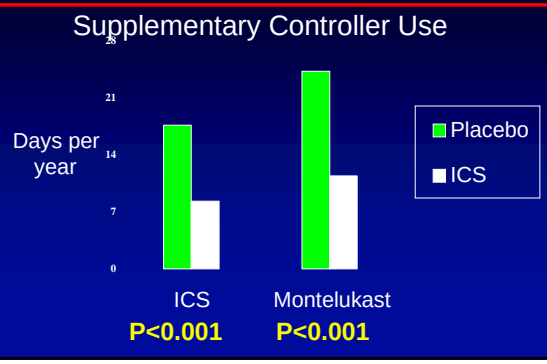
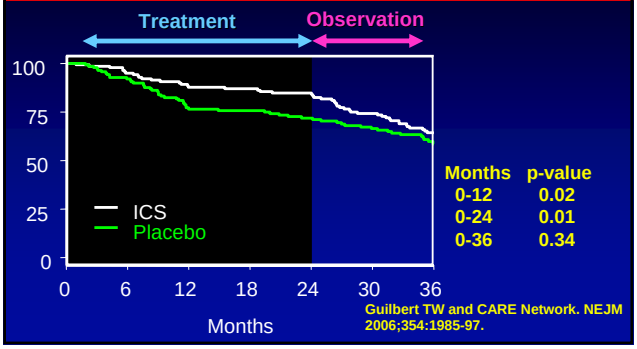
ICS Effect During Treatment Phase



Time to Any Supplementary Asthma Controller Medication



Guilbert TW and CARE Network. NEJM 2006;354:1985-97.

Summary & Clinical Implications

Based on the results of the PEAK study:

- ICS are effective in improving asthma-like symptom burden, exacerbations, and lung function in high-risk toddlers.
- Continuous ICS therapy for 2 years once discontinued does not modify the natural history of asthma in early childhood

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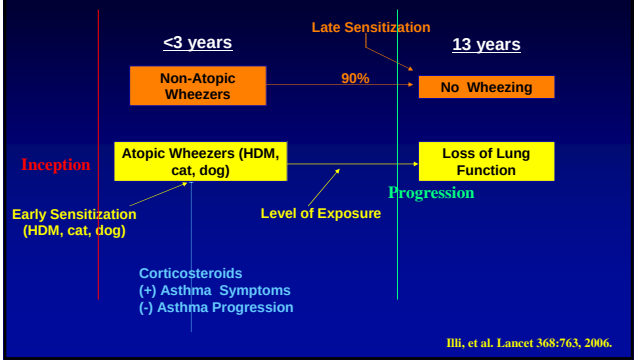
EARLY INTERVENTION STUDIES

	PEAK Guilbert, NEJM, 2006;354:1985	IFWIN Murray, Lancet, 2006;368:754	PAC Bisgaard, NEJM, 2006;354:1998
Number	285	200 (birth cohort and MD referral)	301 randomized (COPSAC birth cohort)
Age	Mean: 3 y Range: 2-3	Median: 1.2 y Range: 0.5-4.9	Mean: 10.6±6.8 mos.
# wheezing	> 3	2 MD dxed or prolonged	>1
Risk	Modified API	Parental atopy	Maternal asthma
Intervention	Daily FP MDI 176 mcg/day	Daily FP MDI 200 mcg/day (step up/step down allowed)	Episodic Bud MDI 400 mcg/day x 2 weeks started on Day 3
1° Outcome	Symptom free days (3rd year)	MD dx asthma by age 5	Sx- free days; persistent wheezing
Duration study	3 years	Up to age 5 years	Up to age 3 years
Ancillary measures	Lung function: IOS, spirometry	Lung function: sRaw; AHR EVH	Lung function: sRaw Rapid volume thoracoabd compression
Growth effects	+	+	-

Natural History of Asthma/Wheezing



Illi, et al. Lancet 368:763, 2006.

Possible Reasons ICS Failed to Alter the Natural History of Asthma

- Intervention not started early enough
  - Treating children younger than age 2 would include many who will outgrow their disease
- Children may not have received a sufficient dose of ICS
- ICS may not alter the natural history of asthma regardless of the time they are initiated

Pediatric Asthma: Early Intervention

- Variability in asthma control should be anticipated
- Reasons for variability should be identified and addressed
- Inhaled glucocorticoids are the preferred first line long-term control therapy
- Inhaled glucocorticoids are effective in alleviating symptoms but do not alter the natural history of asthma.
- Alternative therapies merit investigation as potential interventions following early diagnosis of asthma.

Potential Approaches to Improving Asthma Control

- Early intervention
- Combination therapy
- Biomarkers
- Genetics
- Immunomodulators

Asthma Management

Current status of asthma medications

- Inhaled corticosteroids are the preferred long-term control therapy for persistent asthma, but effect is lost once treatment is stopped.
- LABA is considered the preferred supplementary therapy.
- LTRA is considered an alternative first-line and supplementary therapy.
- Anti-IgE is viewed as blocking IgE effect.
- None are classified as immunomodulator.

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Asthma Management

Individualized Approach

- Utilize asthma characteristics, biomarkers, and genetics to "profile" asthma severity.
- Select medications based on driving factors of disease presentation and predictors of response.
- Monitor response and assess reasons for treatment failure.
- Develop proactive approach and adjust therapy accordingly.