

Confident, Contemporary Management of Pediatric Asthma

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Disclosures

- There are no relevant financial relationships with commercial interests to disclose
- No active research funding
- Several asthma therapies discussed in this talk have limited age-ranges approved by the FDA. I will do my best to call this out.



Asthma: definition & burden

- **Chronic inflammatory disease of the airways occurring at any age, and characterized by airflow obstruction that leads to cough, wheezing, dyspnea and chest tightness.**
- **Prevalence in children worldwide = 14%**
- **> 6 million US children affected, leading to:**
 - **>3 million physician visits,**
 - **>160,000 hospitalizations, and**
 - **>14 million missed days of school per year**



Asthma: heterogeneous and variable

- **Multiple phenotypes and endotypes across patients**

 - Early vs. late onset, mild vs. severe, intermittent vs. persistent
 - Eosinophilic vs. non-eosinophilic, obese vs. non-obese
- **Multiple triggers within one patient**
 - Viruses, allergens, activity, stress, air quality and temperature
- **Age-dependent changes in physiology**
 - Airway growth
- **Inconsistent delivery of pharmacotherapy to site of disease**
 - Access, adherence, device technique, particle size



Objectives

- Discuss asthma heterogeneity - **phenotypes & endotypes**
- Solidify the importance of importance of appropriate inhaled drug **device technique**
- Improve confidence with delivering effective “**step-up**” therapy for poorly controlled patients
- Review established treatments for pediatric asthma and **introduce new therapies**, including: long-acting anticholinergic agents, biologic agents, and digital health

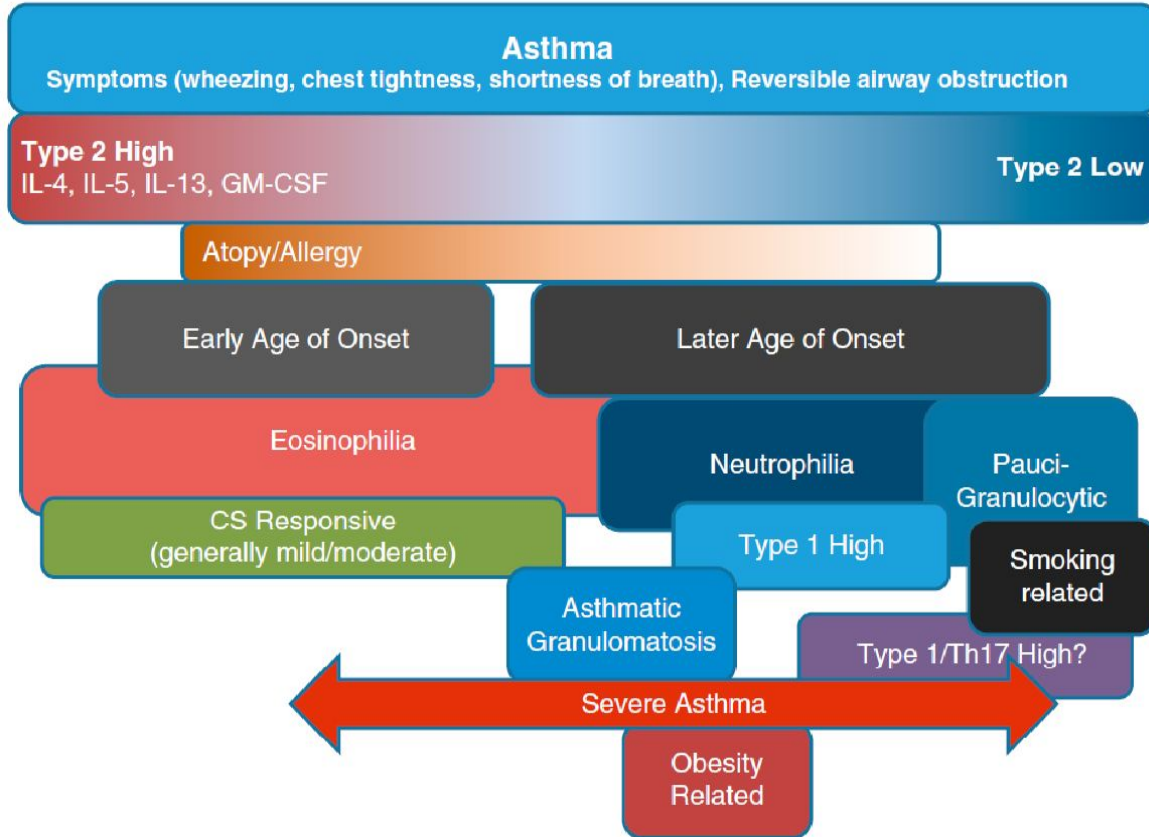


Asthma: heterogeneous and variable

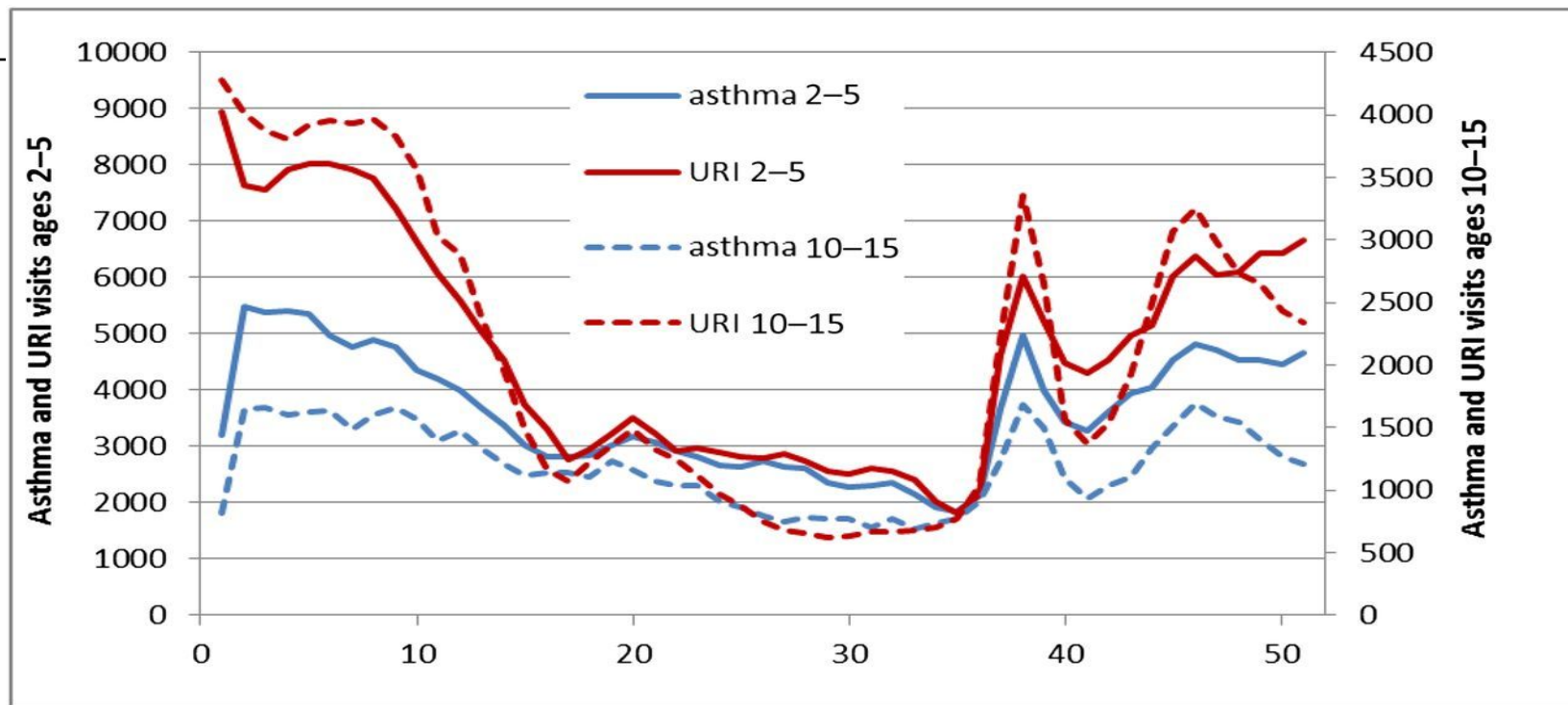
- **Phenotype** – interaction of genetics and environment to generate observable, overlapping characteristics
 - Early vs. Late onset
 - Triggers (exercise-induced, viral, atopic, etc.)
 - Symptom frequency (intermittent, persistent) and severity (FEV1)
 - Associated comorbidities (obesity, smoking, etc.)
- **Endotype** – underlying cellular pathobiology
 - T-helper lymphocyte type 2 (Th2)-high or Th2-low
 - Eosinophilic vs. neutrophilic vs. mixed



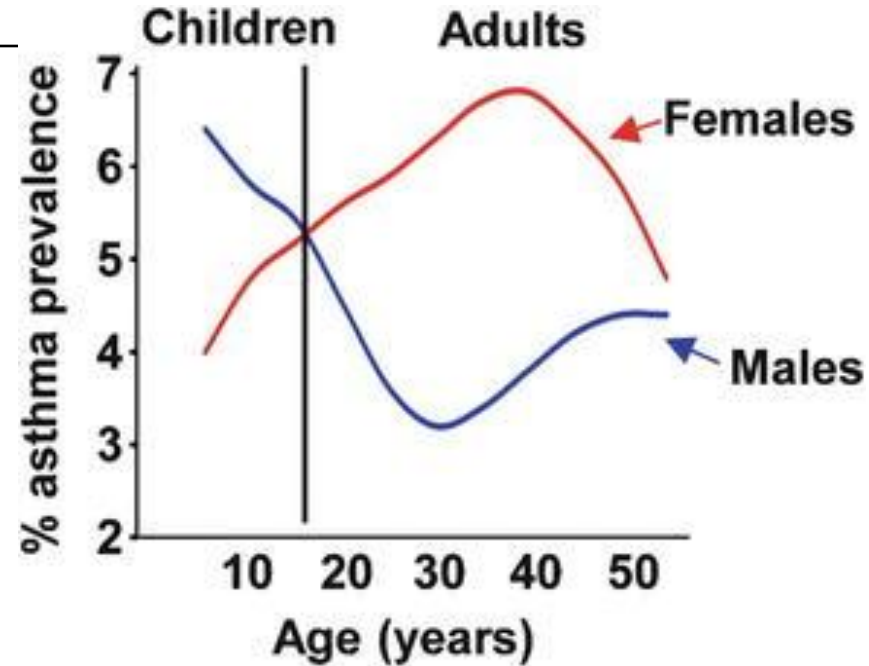
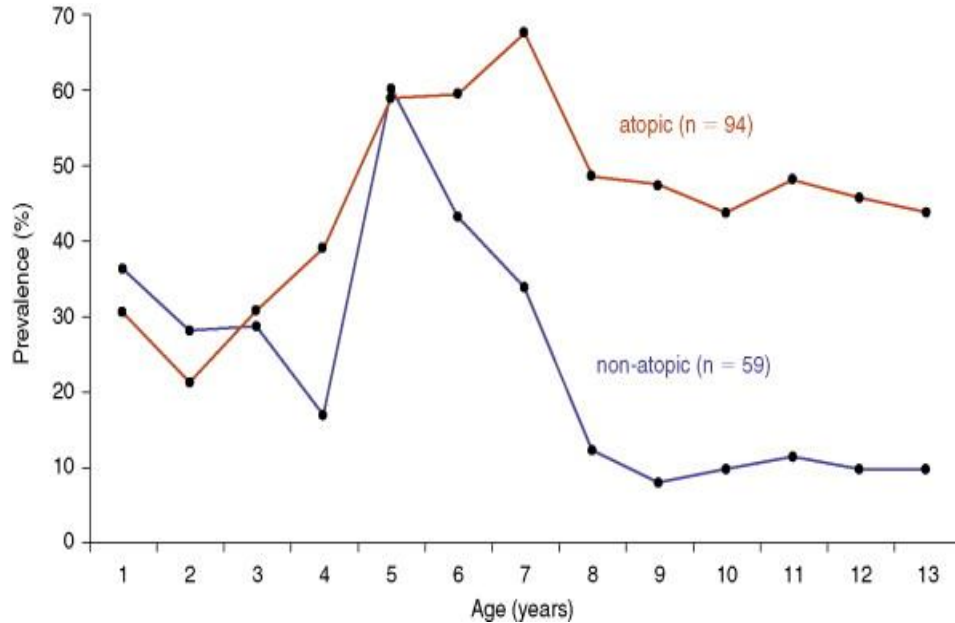
Asthma: heterogeneous and variable



Asthma: heterogenous and variable



Asthma: heterogeneous and variable



Asthma: tried and true treatments

- Short-acting beta-agonists
- Inhaled corticosteroids
- Long-acting beta-agonists
- Leukotriene modifiers
- Anticholinergics
- Antihistamines
- Systemic corticosteroids



Asthma: tried and true treatments

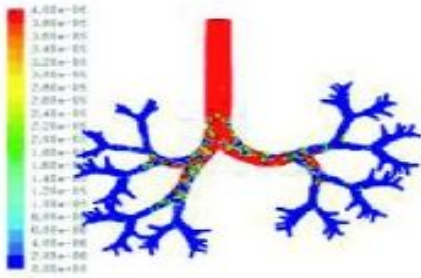


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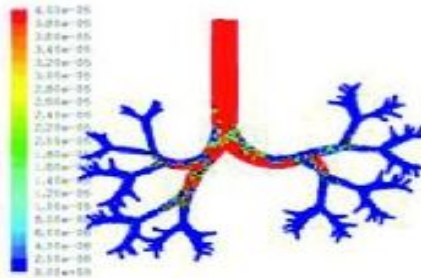
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Inhaled drug delivery

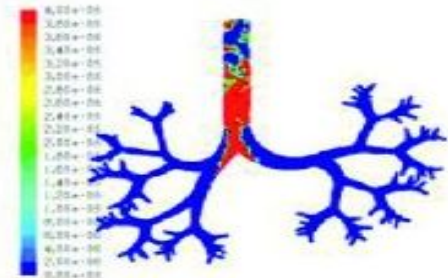
Even under **ideal** conditions, it's less than ideal



30-60%

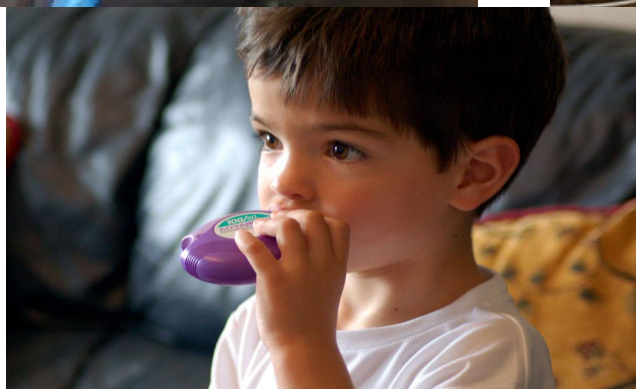


15-30%



5-10%

Inhaled drug delivery



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Inhaled drug delivery



Nebulizers

- Require compressor, tubing, drug chamber, delivery interface
- Mask held in contact with face
- Mouthpiece with lips closed
- No “blow by”



Inhaled drug delivery



© Healthwise, Incorporated

Metered Dose Inhalers (MDIs)

- Propellant delivers drug plume from pressurized canister
- **Spacer** always recommended
- +Mask for patients <7-8yrs
 - 6 tidal breaths
- +Mouthpiece once able
 - One large breath and hold



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Inhaled drug delivery



Combivent®
(albuterol /
ipratropium)

Spiriva®
(tiotropium)



Breath Actuated MDIs & RespiMat® soft plume

- Require low inspiratory flow rates
- Not used with spacers
- Limited pediatric data



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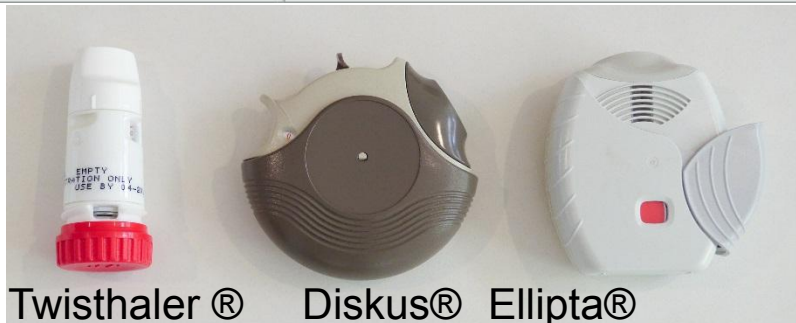
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Inhaled drug delivery

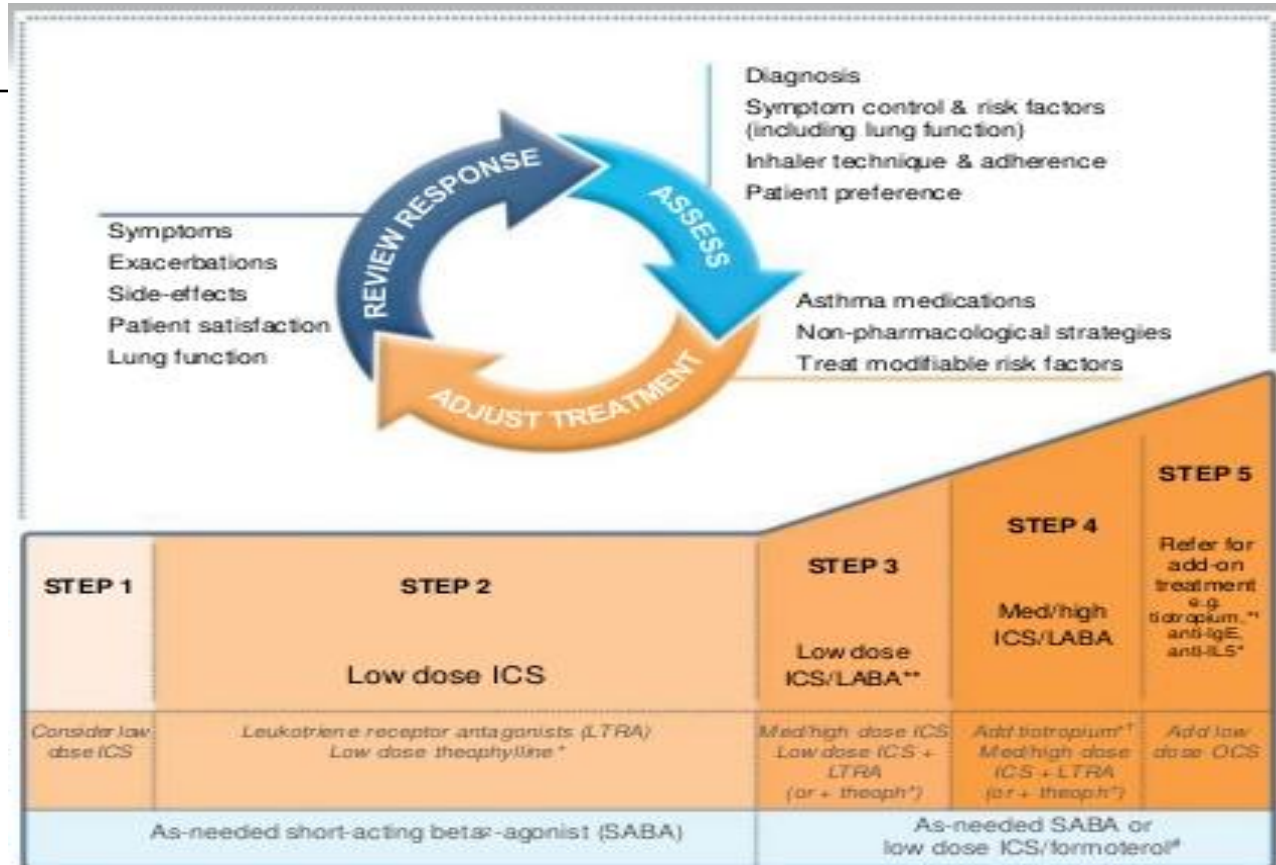
Device	Optimal peak inhalation flow rate (PIFR) for powder dispersion
Respimat [®] , pMDI	Lower is better
Clickhaler [®]	> 20 L/min
Handihaler [®]	
Swinghaler [®]	
Twincaps [®]	
Diskus [®]	> 30 L/min
Ellipta [®]	
Turbuhaler [®]	
Twisthaler [®]	
Jenuair [®]	> 45 L/min
Breezhaler [®]	> 50 L/min
Diskhaler [®]	> 60 L/min

Dry Powder Inhalers (DPIs)

- Require higher inspiratory flow rates
- Must be held at optimal angle
- Do not use with spacer



Global Initiative for Asthma (GINA) Guidelines



The pediatric asthma yardstick

Practical recommendations for a sustained step-up in asthma therapy for children with inadequately controlled asthma

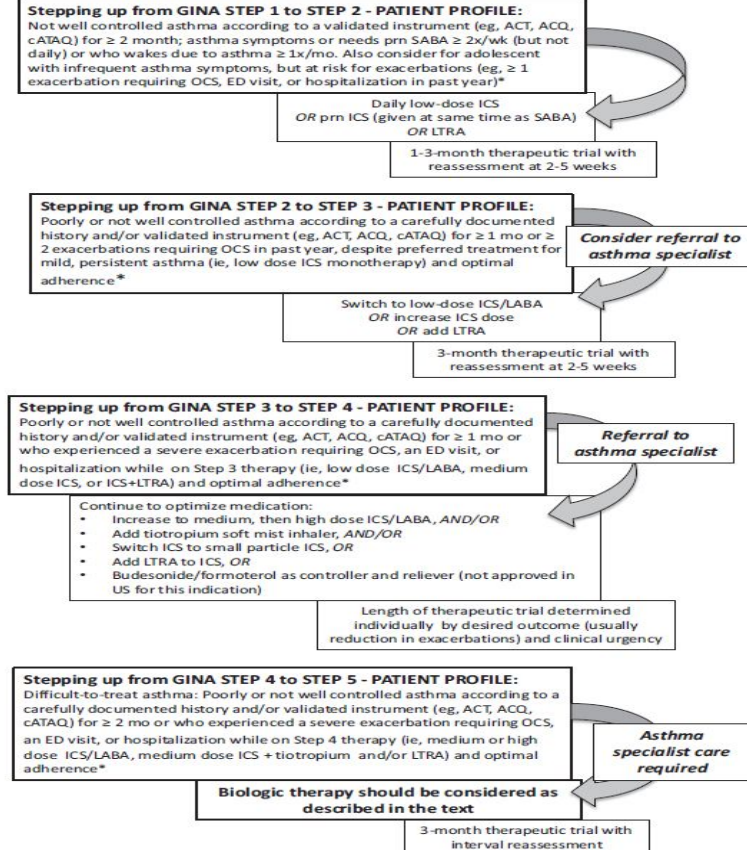
Bradley E. Chipps, MD ^{*}; Leonard B. Bacharier, MD [†]; Judith R. Farrar, PhD [‡]; Daniel J. Jackson, MD [§];
Kevin R. Murphy, MD ^{||}; Wanda Phipatanakul, MD, MS [¶]; Stanley J. Szefler, MD [#];
W. Gerald Teague, MD ^{**}; Robert S. Zeiger, MD, PhD ^{††}

Annals of Allergy Asthma and Immunology, 2018



The Pediatric Asthma Yardstick

Adolescents



Guidelines by age group

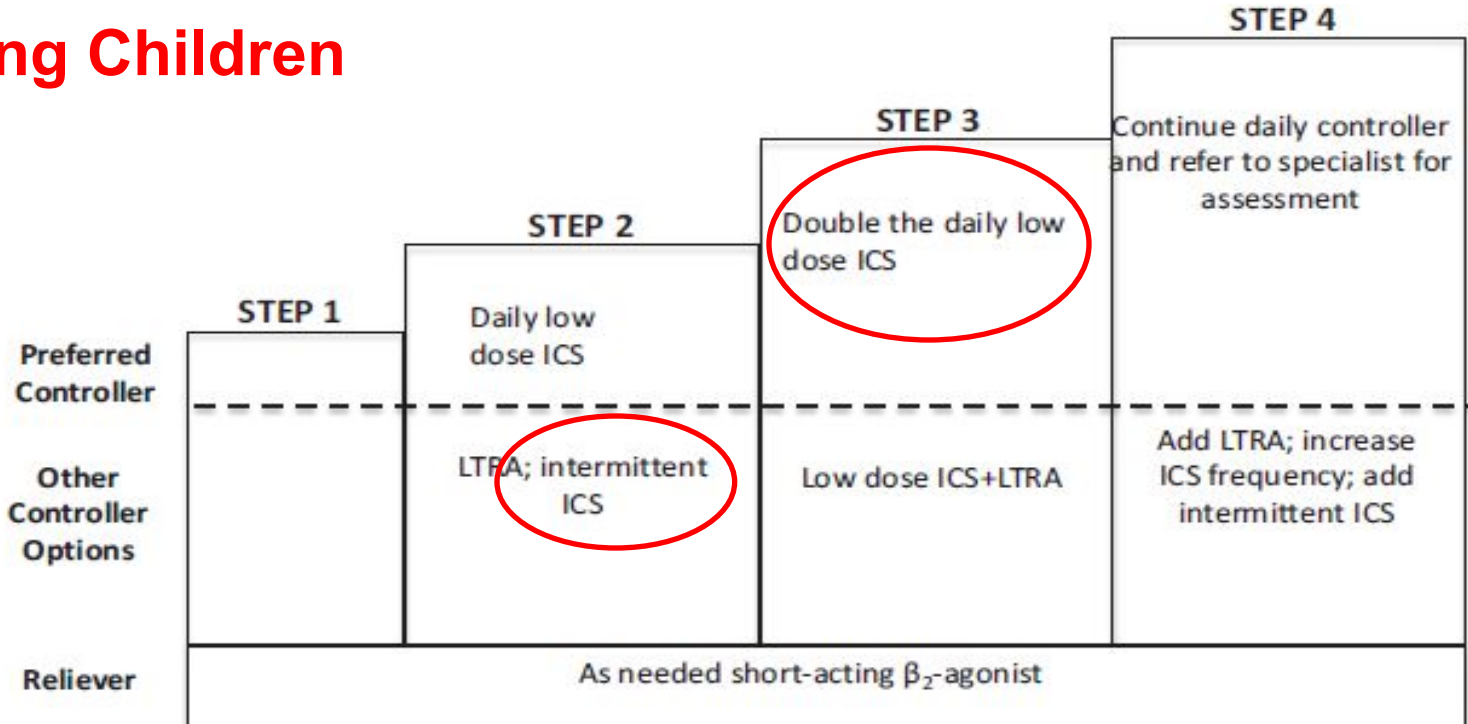
Patient profiles

Clear next steps

When to refer

The Pediatric Asthma Yardstick

Young Children

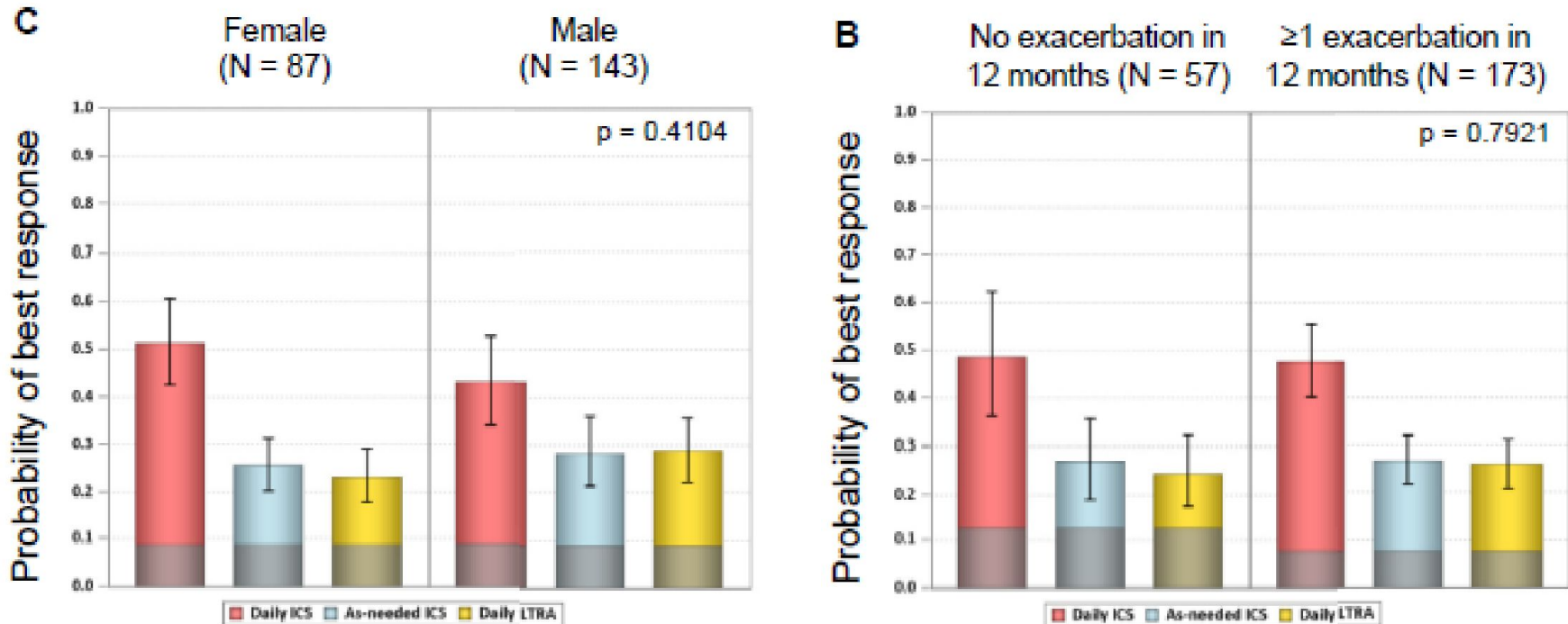


ICS = inhaled corticosteroids



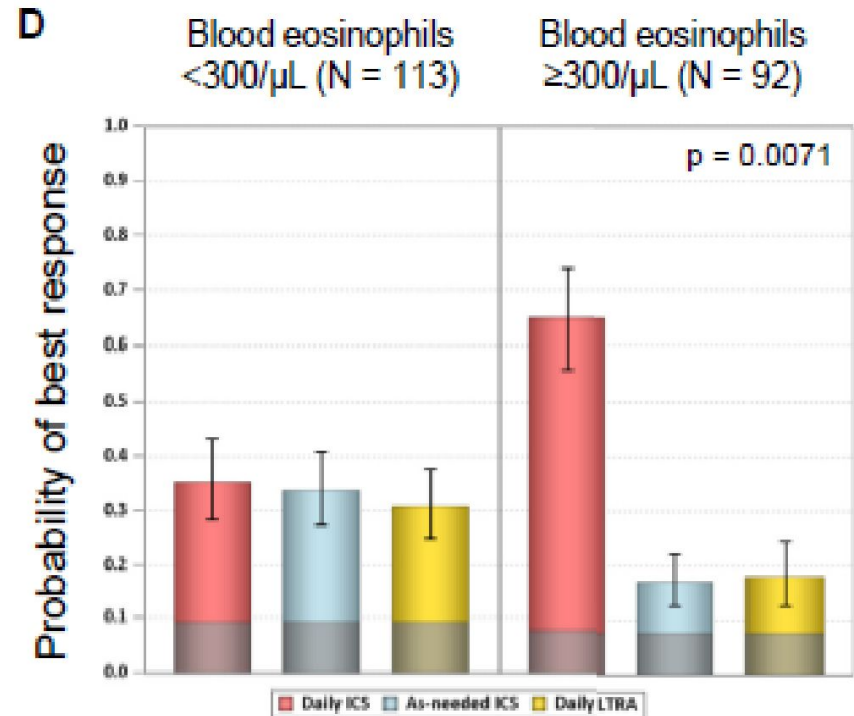
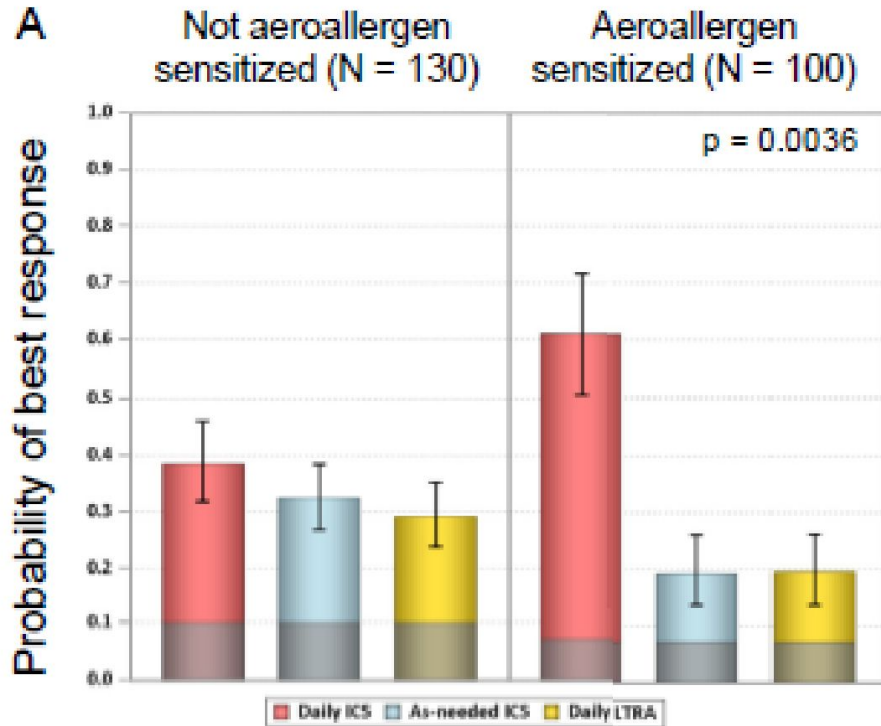
Stepping-Up: infants and young children

Fitzpatrick et al. J Allergy Clin Immunol, Dec 2016



Stepping-Up: infants and young children

Fitzpatrick et al. J Allergy Clin Immunol, Dec 2016

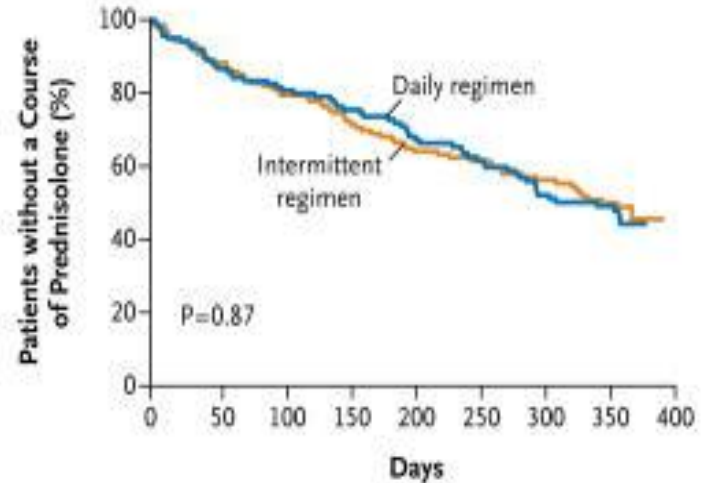


Episodic ICS in preschool wheeze

Zeiger et al. NEJM, Nov 2011

- 278 children, age 1-4.5yrs
- Randomized trial -
 - Budesonide 0.5mg neb daily, or
 - 1mg neb BID x7 days when sick
- Rate of exacerbations needing prednisone similar (and low)
- Time to first exacerbation same
- Symptom pattern, parental missed work not different

B Time to First Exacerbation

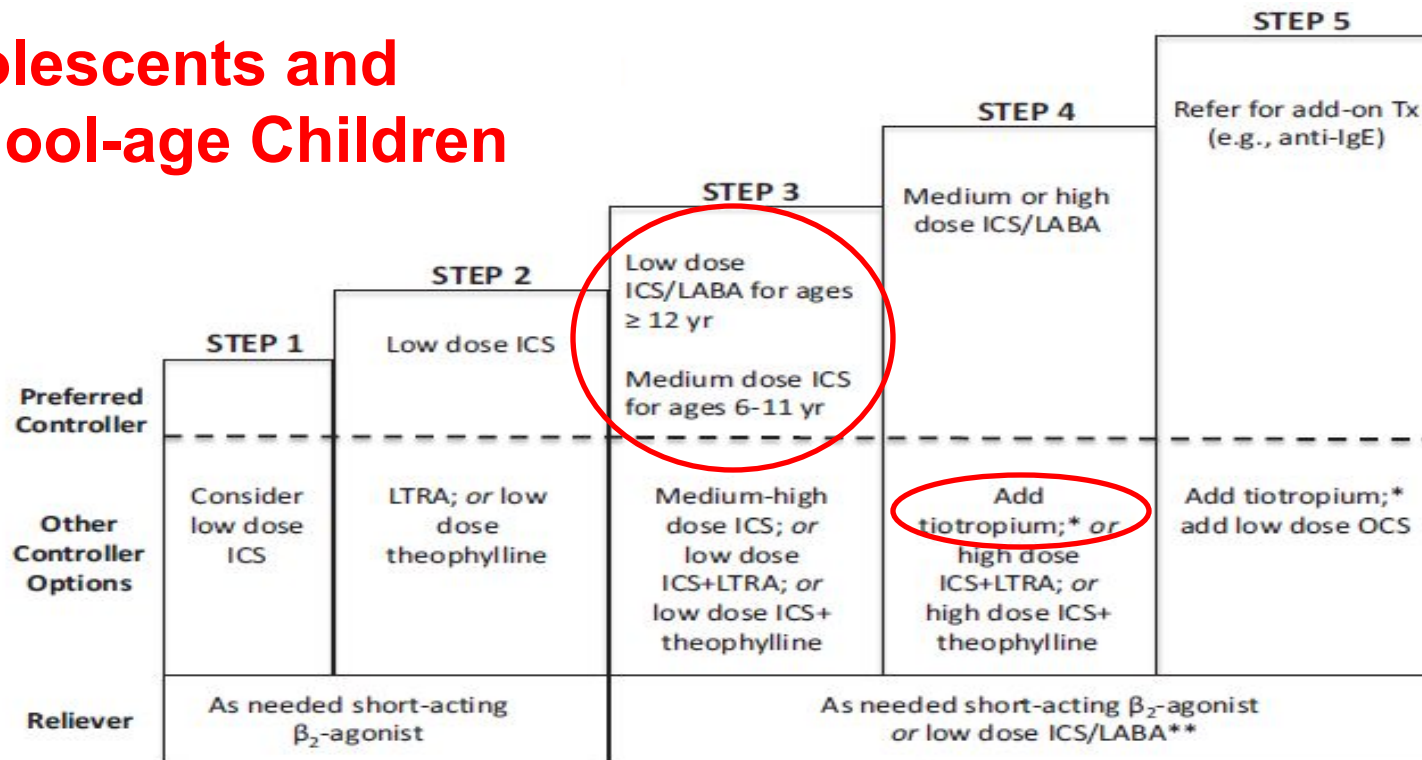


No. at Risk

Intermittent regimen	139	114	100	89	78	71	64	50
Daily regimen	139	114	93	84	74	66	54	40

The Pediatric Asthma Yardstick

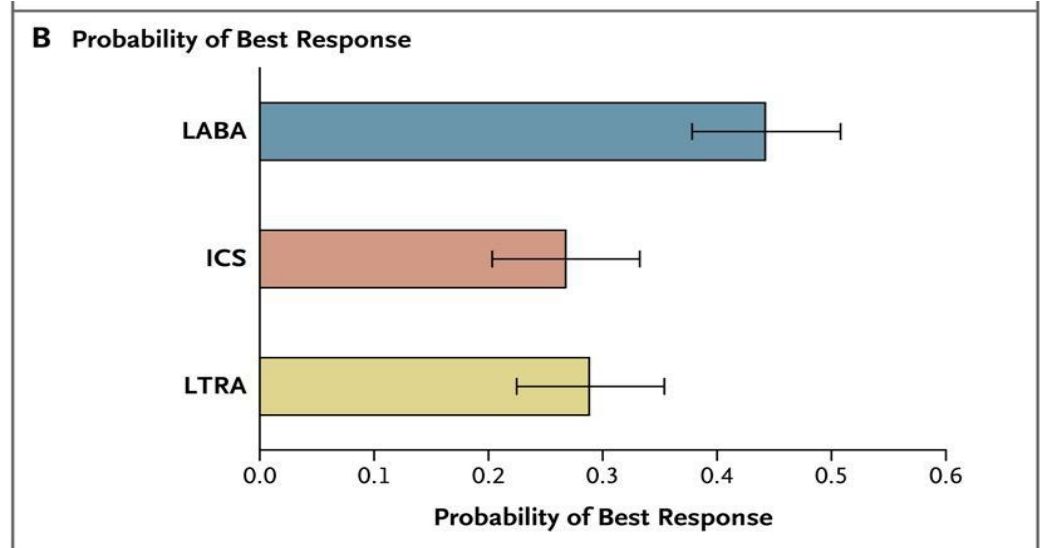
Adolescents and School-age Children



Stepping-Up: school age - adolescent

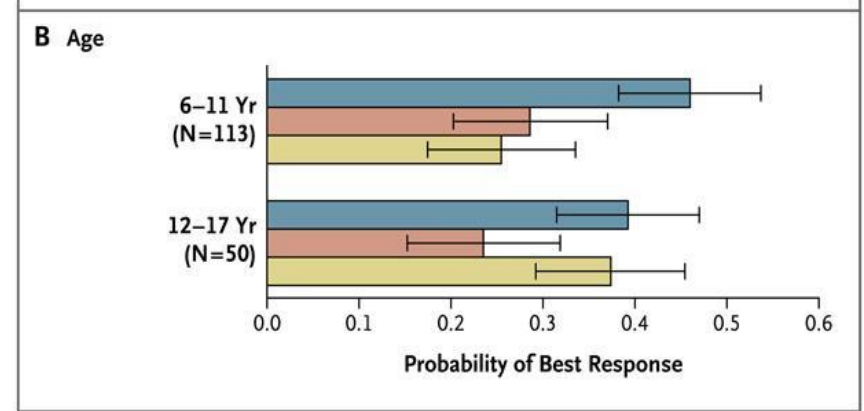
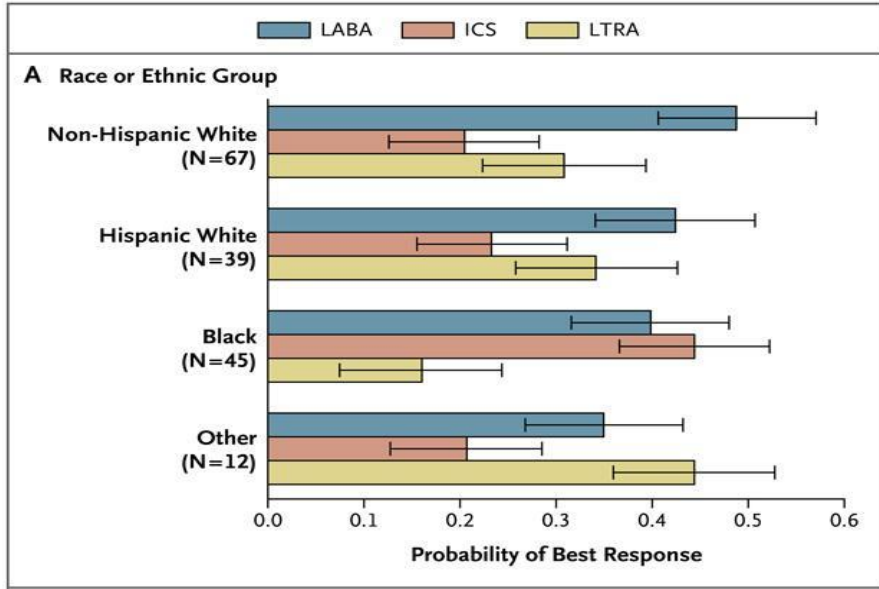
Lemanske et al. NEJM, Mar 2010

- 182 children, **6-17 years**
- Mild persistent asthma with poor control
- Low dose daily ICS (fluticasone 100mcg BID)
- Randomized, 3x cross-over
 - Δ 250mcg fluticasone**
 - + 50 mcg salmeterol**
 - + 5-10mg Singulair**



Stepping-Up: school age - adolescent

Lemanske et al. NEJM, Mar 2010



Differential response by race/ethnic group was statistically significant, by age group was not.

Long-acting beta agonists (LABAs)

- Multiple meta-analyses now indicate LABAs are safe **when used in combination** with ICS across all ages studied.
- Black box warning removed by FDA December 2017

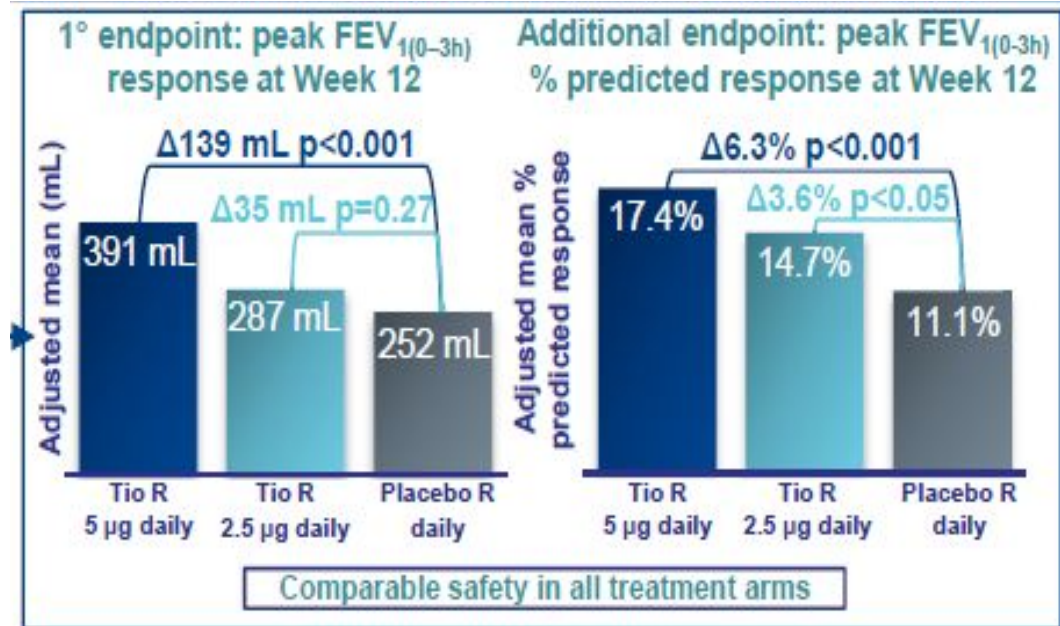
WARNING

WARNING: Long-acting beta₂-adrenergic agonists (LABA), such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABAs, including formoterol. Current available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term controller drugs mitigates the increased risk of asthma-related death from LABA. **Additional data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalizations in pediatric and adolescent patients**

Tiotropium

Szeffler et al. J Allergy Clin Immunol, Feb 2017

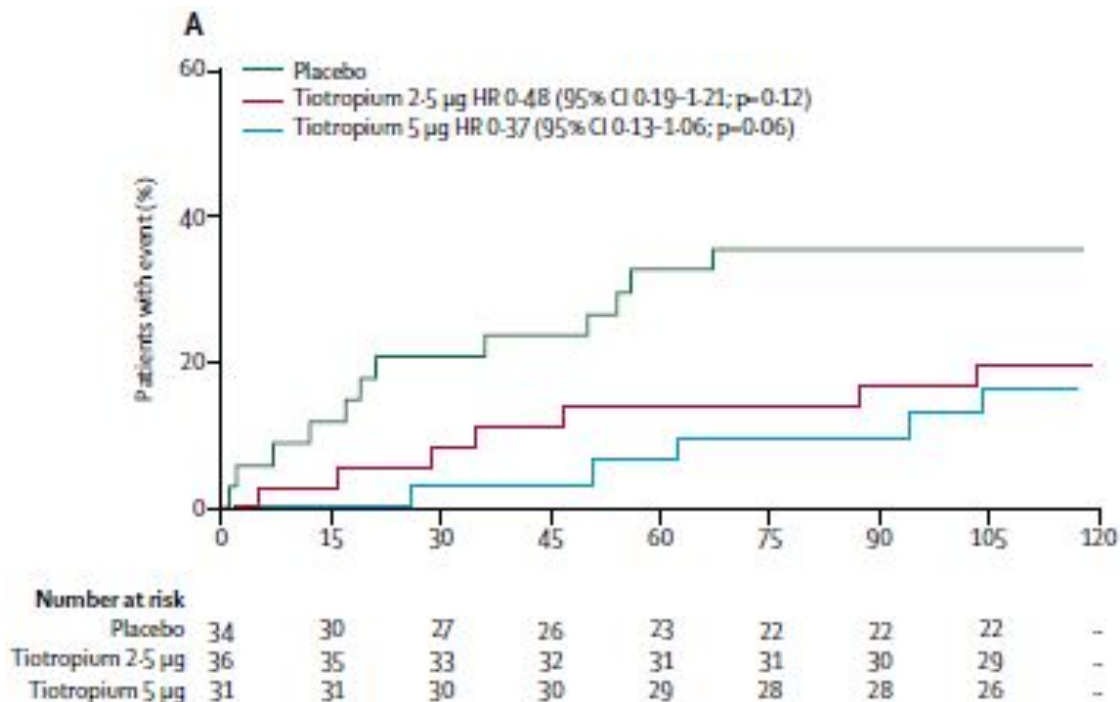
- 401 children, **age 6-11yrs**
- High dose ICS, or medium dose ICS + LABA/LTRA
- Tiotropium 2.5 or 5mcg, or placebo x 4 months
- Primary endpoint = peak and trough FEV_1



Tiotropium

Vrijlandt EJ, et al. Lancet Respir Med, Feb 2018

- 102 children, **age 1-5yrs**
- Daily ICS
- Tiotropium 2.5 or 5mcg, or placebo x 4 months
- *Trend* in reduction of time to first exacerbation or worsening
- No difference in daily symptoms



Short-term ICS dose increase

Jackson et al. NEJM, March 2018

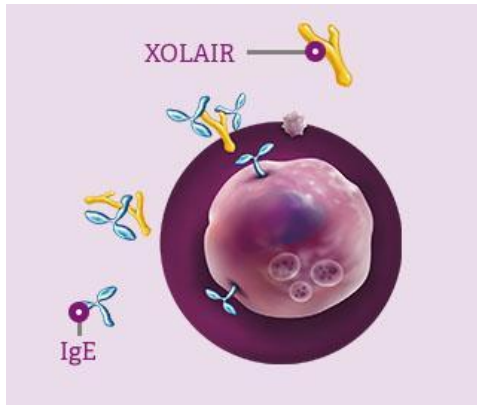
- 254 children, 5-11 years
- Randomized Trial –
 - Flovent 44mcg BID, no increase
 - Increase to 220mcg BID with illness

Significant slowing of growth velocity seen in 5-7 year old age group

Outcomes	Low-Dose Group (N= 127)	High-Dose Group (N= 127)	Treatment Effect (95% CI) [†]	P Value
Primary outcome				
No. of exacerbations per year (95% CI)	0.37 (0.25 to 0.55)	0.48 (0.33 to 0.70)	1.3 (0.8 to 2.1)	0.30
Secondary outcomes				
No. of emergency department or urgent care visits per year (95% CI)	0.47 (0.31 to 0.72)	0.64 (0.42 to 0.96)	1.3 (0.8 to 2.4)	0.30
No. of hospitalizations	0	4	—	0.12

Biologics

- **Omalizumab (Xolair®)**
 - **Anti- IgE**
 - FDA approved \geq **6yrs**
 - SQ injection, 2-4 weeks
 - IgE must be in range
- **Mepolizumab (Nucala®), Benralizumab (Fasenra®)**
 - **Anti- IL-5** (eosinophils)
 - FDA approved \geq **12yrs**
 - SQ injection, 4 weeks
 - Evidence of eosinophilia (blood, FeNO, sputum)



Digital Health

Sleurs K, et al. *Allergy*, Jul 2019

- 71+ available Asthma “apps” for iOS and Android
- 80% by medical tech companies, 18% by MDs
- 80% free, 20% language other than English

- 2/3 offer disease self-monitoring, 50% with graphs / trends
- 6 with dose-sensing devices, 50% with reminder alerts
- 60% shareable with health care provider



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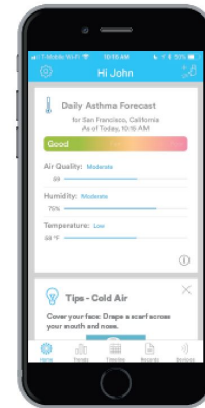
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Digital health

- In Dec 2018, SCH launched a partnership with **Propeller Health** for remote monitoring of asthma care
- No cost to families, no smart phone required
- Eligible patients
 - Persistent asthma with poor control
 - ≥ 2 ED or urgent care visits
 - Hospitalized in last year

remotecare@seattlechildrens.org

seattlechildrens.propellerhealth.com



Final Thoughts

- Pediatric asthma therapy requires personalization
- Differential response to therapy between patients is almost universal
- Evaluating symptoms, environmental factors, adherence and device technique at every visit is critical, as disease can change within each patient over time



Final Thoughts

- **For young children –**
 - Mild symptoms may be managed with daily or intermittent ICS
 - LTRA may be considered, with evaluation of response
 - More severe symptoms require daily ICS, with escalation of dose
- **For older children & adolescents –**
 - Daily ICS is gold standard for initial therapy
 - Poor control is most likely to respond to addition of LABA
 - Certain ethnic groups may respond better to higher ICS or LTRA
 - Tiotropium should be considered in difficult to control asthma

Questions



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Extra slides

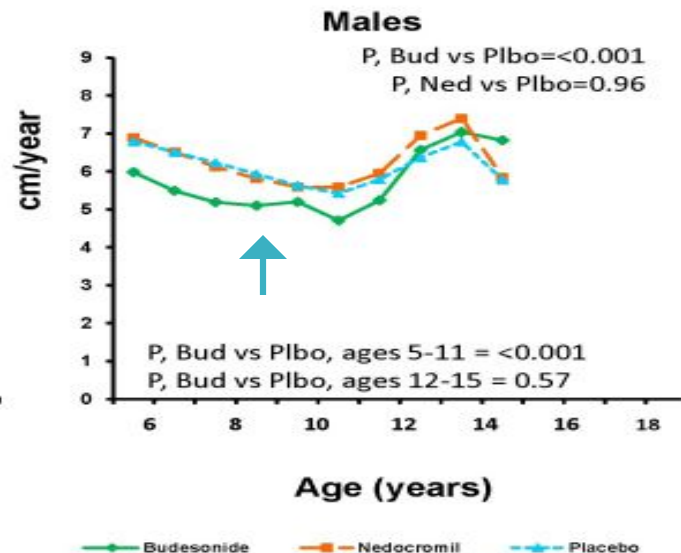
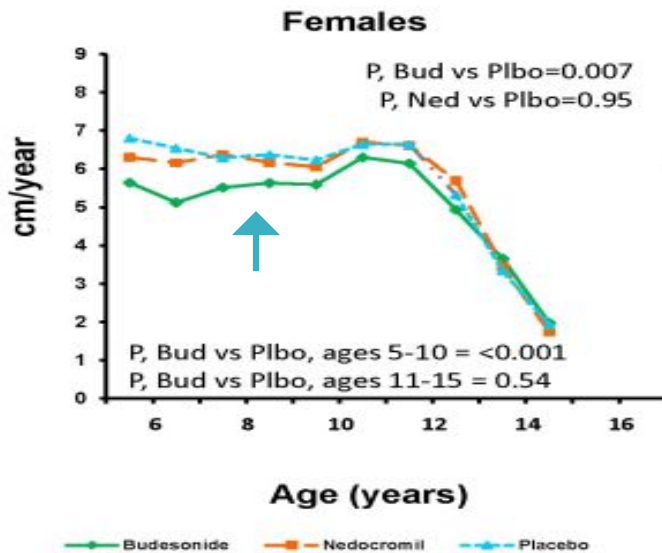


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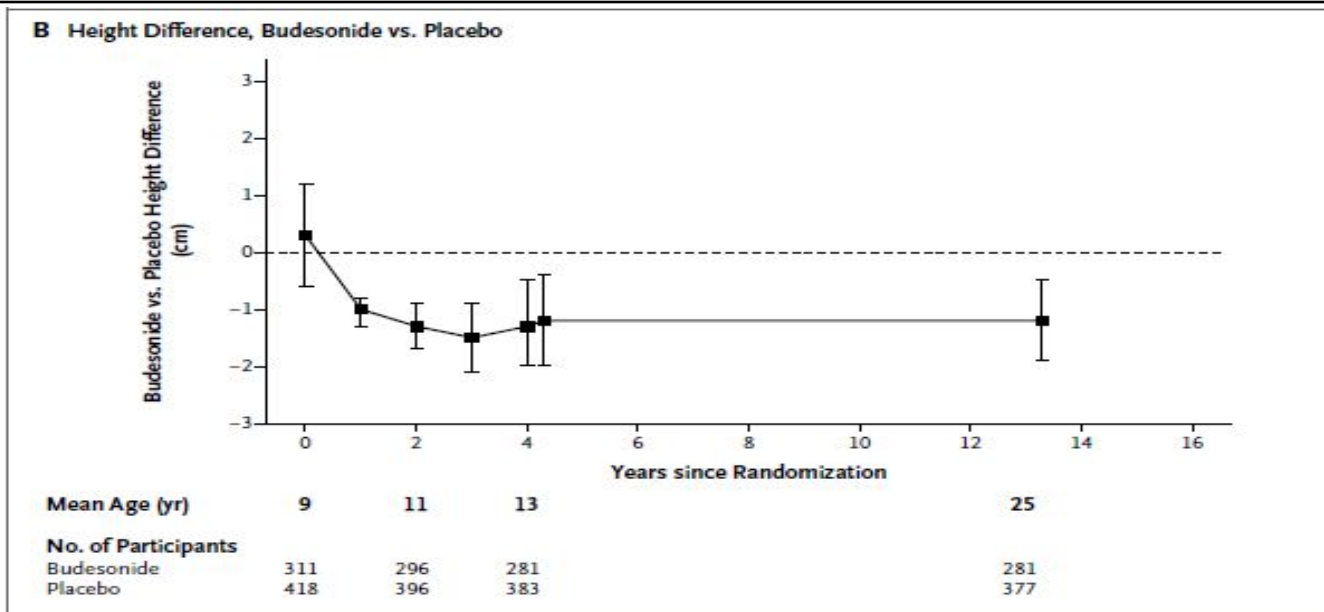
ICS & Growth

CAMP Research Group. NEJM Oct 2000



ICS & Growth

Kelly HW et al. NEJM Sept 2012



Long-acting beta agonists (LABAs)

Jorup C, et al. Eur Respir J, Jan 2018

- Multiple studies have evaluated the use of ICS+LABA as maintenance plus rescue therapy in adolescents and adults
- Time to first exacerbation and symptoms reduced, similar acute events

