Recurrent Wheezing in Preschool Children

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Disclosure

- I have nothing to disclose related to this talk.

Background / Objectives

- Asthma is the most common chronic disease of childhood
- Recurrent wheezing is common among preschool children
- The pathophysiology and treatment of these preschool episodes is likely different than those for older children or adults with well-established asthma
- This talk will focus on new advances in the treatment of these children with a direction towards personalized medicine

Preschool Wheezing – Scope of Problem

Tucson Children's Respiratory Study
Birth cohort of 826 children with follow up data at 2 points

<u>0-3 years:</u> Physician Diagnosis of LTR illness with wheeze?	**<u>6 years:</u> Current wheezing?**	
No	**No**	**Never Wheeze (51.5%)**
Yes	**No**	**Transient Early Wheeze (19.9%)**
Yes	**Yes**	**Persistent Wheeze (13.7%)**
No	**Yes**	**Late Onset Wheeze (15.0%)**

Martinez FD, NEJM, 1995

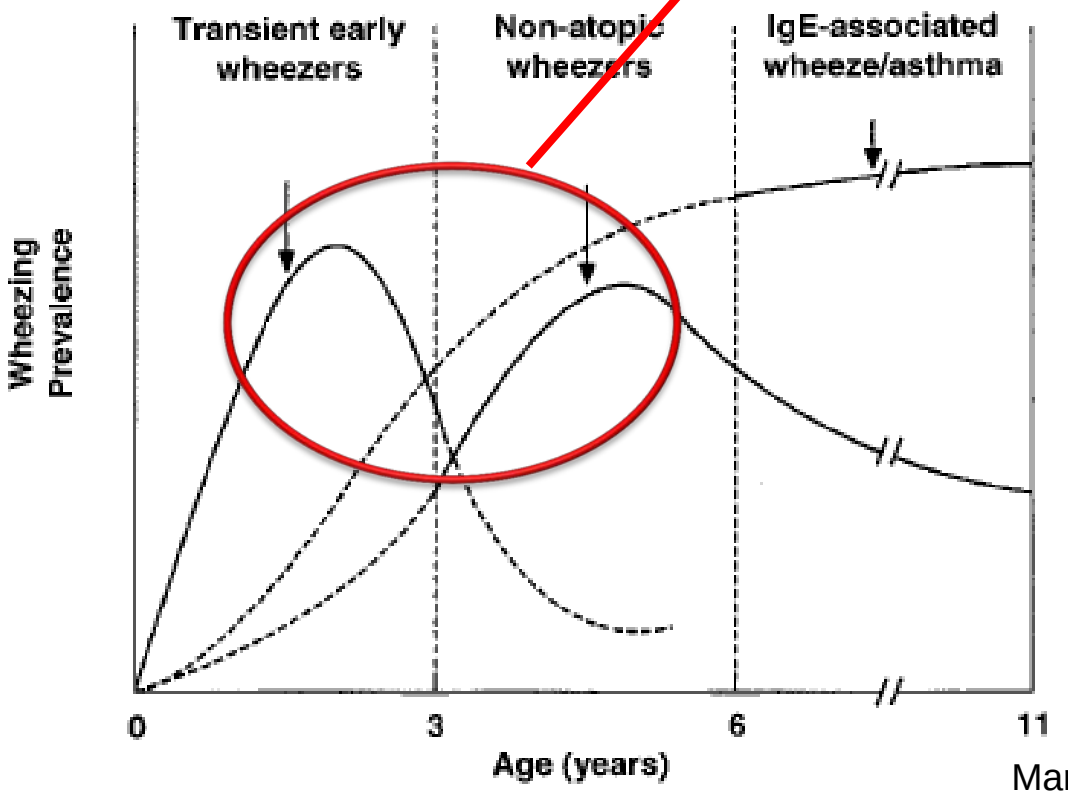
Preschool Wheezing – Scope of Problem

- Approximately 50% of children had wheezing episode at some point in first 6 years of life.
- Almost 60% of those with wheeze in the first 3 years of life had outgrown this condition by 6 years of age.
- Transient Early Wheeze were more likely to have:
  - Diminished airway function at birth
  - Mothers who smoked, but not mothers with asthma
- Persistent Wheeze were more likely to have:
  - Mother with a history of asthma
  - Atopy: elevated serum IgE levels, eczema, rhinitis, + skin testing

Martinez FD, NEJM, 1995

Preschool Wheezing – Phenotypes

At ages 2-5 years, all three of these phenotypes are prevalent… should we be treating children differently?



Martinez FD, Pediatrics, 2002

Preschool Wheezing – Scope of Problem

- Preschool wheezers have the highest rates of healthcare utilization including:
  - ED visits
  - Hospitalizations
- Goal is to implement personalized strategies in these children in order to control symptoms and/or prevent exacerbations

Akinbami L, Pediatrics, 2009

Children with Episodic Wheezing Episodes vs. Children with Persistent Symptoms

- The best place to start for personalized medicine for these children is to differentiate children with intermittent disease from children with persistent disease.

- **Intermittent Disease:**
  - Children with recurrent flares of wheezing episodes
  - High health care utilization – ED visits, hospitalizations
  - Healthy in between episodes, minimal day-to-day symptoms

- **Persistent Disease:**
  - >2 days/week, 1-2 nights/month, limitations on normal activities
  - +/- more severe wheezing exacerbations

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Preventing Exacerbations in Preschoolers With Recurrent Wheeze: A Meta-analysis

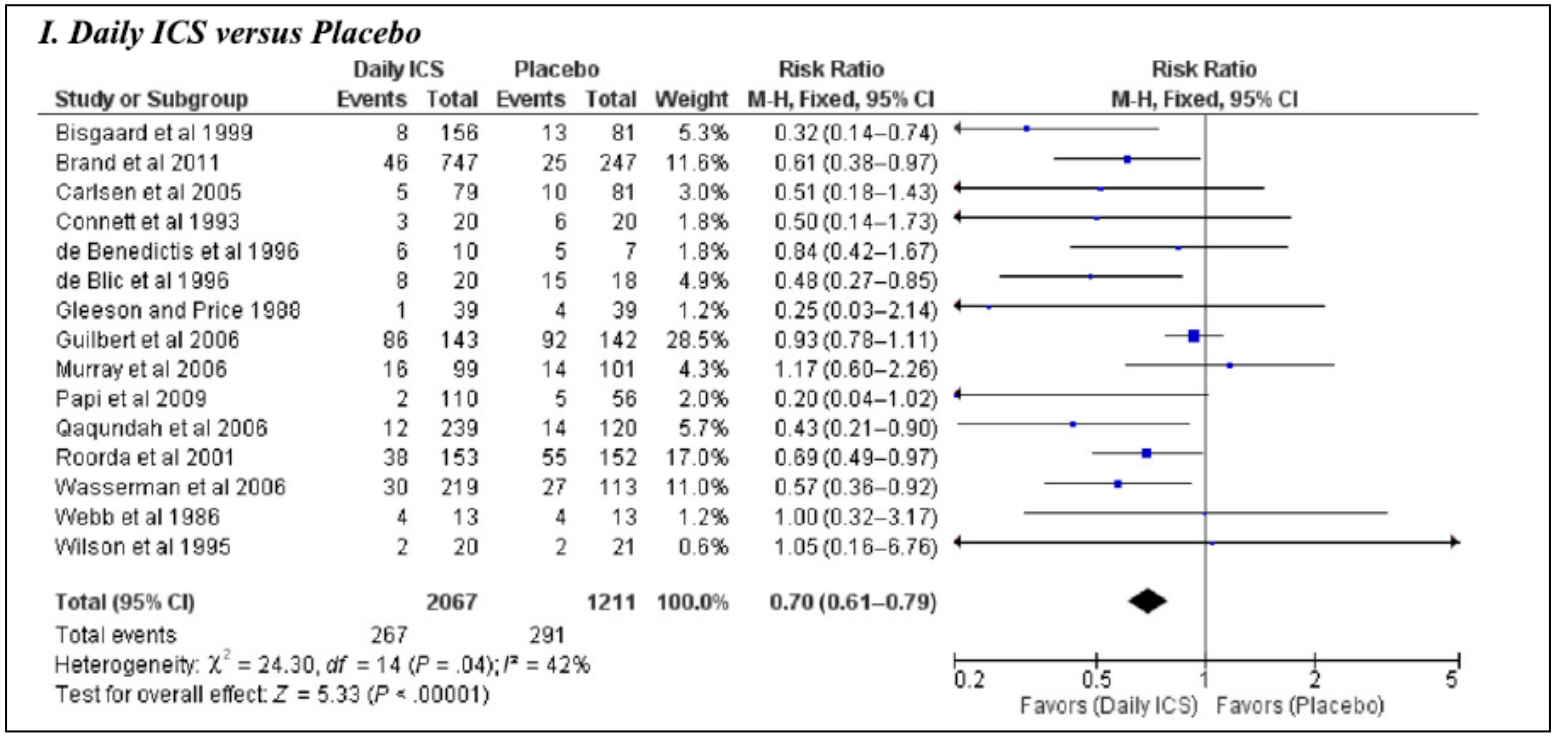
Sunitha V. Kaiser, Tram Huynh, Leonard B. Bacharier, Jennifer L. Rosenthal, Leigh Anne Bakel, Patricia C. Parkin and Michael D. Cabana

Pediatrics 2016;137;

- Recent meta-analysis that examined the current evidence of the use of daily ICS, intermittent ICS, or montelukast
- Focused on children with episodic wheezing episodes
  - Some analyses on children with more persistent disease
- Focused on the outcome of preventing exacerbations

Daily ICS for Episodic Wheezing Episodes

- 30% reduction in the risk of exacerbation requiring systemic corticosteroids
- Number Needed to Treat (NNT): 9



Kaiser SV, Pediatrics, 2016

Prevention of Episodic Wheezing Episodes

- **Daily ICS vs. Placebo:**
  - 30% reduction in risk of exacerbation, NNT = 9
- **Intermittent ICS vs. Placebo:**
  - 36% reduction in risk of exacerbation, NNT = 6
  - High Doses: Budesonide 1 mg BID, Fluticasone 0.75 mg BID
  - First sign of URTI and continued for 7 days or until asymptomatic
- **Daily ICS vs. Intermittent ICS**
  - No significant differences in outcomes
  - Daily dosing was associated with increased exposure to ICS
  - Only 2 studies included

Kaiser SV, Pediatrics, 2016

Treatment of Children with Persistent Symptoms

- **Daily ICS vs. Placebo:**
  - 44% reduction in risk of exacerbation, NNT = 11

- **Daily ICS vs. Daily Montelukast:**
  - 41% reduction in risk of exacerbation for those on Daily ICS
  - Only one study included

Kaiser SV, Pediatrics, 2016

Summary of Recent Meta-Analysis

- These analyses confirmed the role of ICS as the first-line therapy for preschool wheezers.
- Daily ICS therapy should be considered for preschool children with persistent disease.
- Intermittent ICS (pre-emptive high-dose) is a reasonable option for preschool children with intermittent disease.

Kaiser SV, Pediatrics, 2016

Biomarkers to Predict Success?

- **Step 1:** Differentiate intermittent vs. persistent disease
- **Step 2:** Biomarkers (?)
- Are there useful biomarkers that can predict successful response to the common therapies in this age group?
- A recent clinical trial attempted to answer this question.

INFANT Trial (NHLBI AsthmaNet)

- 300 children (ages 1-4 years)
- Persistent symptoms
  - Meeting criteria for Step 2 therapy (controller)
- Multicenter, blinded, randomized

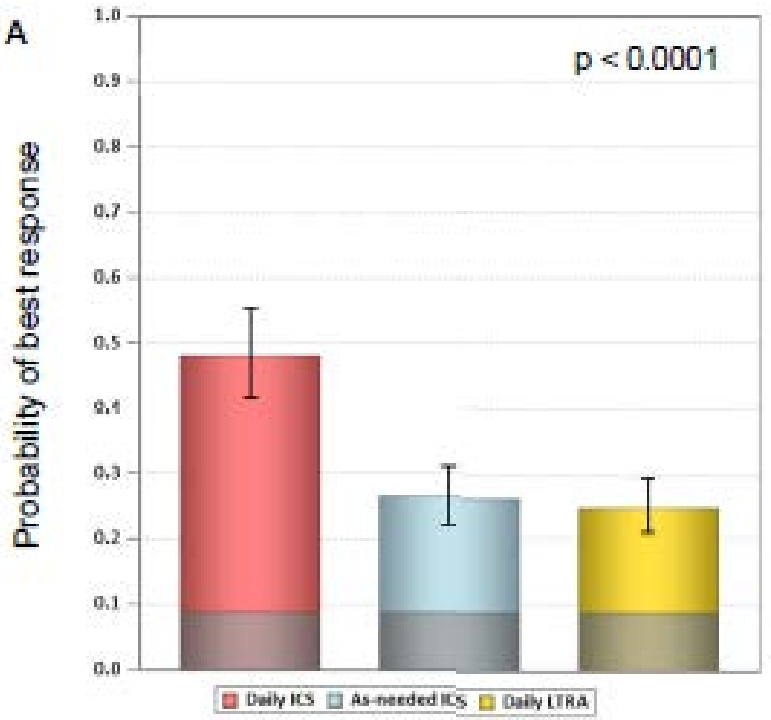
- Triple cross-over of three therapies (16 weeks each):
  - Daily ICS
  - Intemittent ICS
  - Daily Montelukast

- Primary Analyses:
  1. Did children have a differential response to these treatments?
     (composite of exacerbations and daily symptoms)
  2. Are there factors that are able to predict a differential response?

Fitzpatrick AM, JACI, 2016

Daily ICS was most likely the preferred therapy when all children were combined

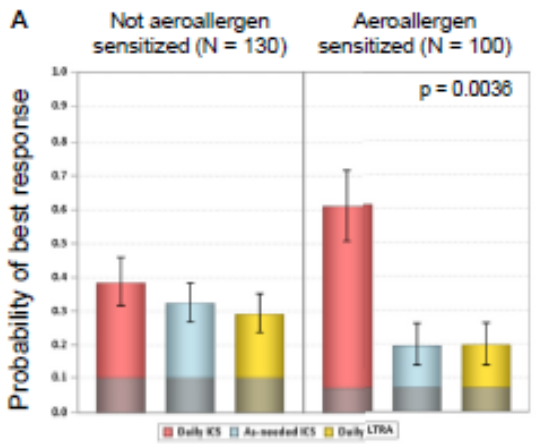
- 74% of children had a preferred response to one treatment
- Daily ICS was most likely the preferred treatment
- Some children did have a preferential response to Intermittent ICS and Daily LTRA
- 26% of children had no preferred choice (less severe)

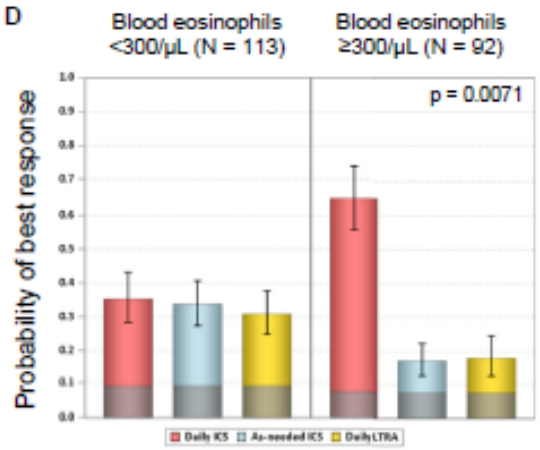


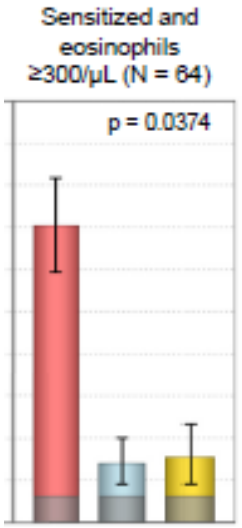
Fitzpatrick AM, JACI, 2016

Aeroallergen Sensitization and Eosinophilia predicted better response to Daily ICS

- Children with one or both of these biomarkers had a preferred response to Daily ICS
- Children without these biomarkers had no preference among the three treatments







Fitzpatrick AM, JACI, 2016

Summary of the INFANT Trial

- Determining peripheral blood eosinophil counts and/or aeroallergen sensitivity may aid clinicians in choosing initial therapy for persistent asthma in preschoolers.
  - Positive testing → Child most likely to respond to Daily ICS
  - Negative testing → Child may be tried on any of the therapies
- If a child does not respond to the initial Step 2 controller therapy, an alternative Step 2 therapy should be considered before escalating to step 3 therapy.

Fitzpatrick AM, JACI, 2016

Other Predictors of Success with Daily ICS

- Previous post-hoc analysis demonstrated that the following factors were also associated with a more favorable response to daily ICS:
  - Boys
  - White
  - More symptoms at baseline
  - ED visit or hospitalization within the past year
  - Aeroallergen sensitization

Bacharier LB, JACI, 2009

Limitations of the Use of ICS

- ICS reduces the rate of exacerbations by approximately 30-40%, but does not completely prevent exacerbations.
- Daily ICS therapy has been associated with a small, but statistically significant, reduction in linear growth.
- Suboptimal adherence to Daily ICS is well documented.
- Is there a better way to treat children without persistent disease, but instead with only recurrent wheezing episodes especially those that are triggered by infections?

Macrolides as a treatment for asthma

- Macrolides have been shown to have beneficial anti-inflammatory effects in other inflammatory chronic lung disease.
- Macrolides reduce neutrophilic inflammation which is prominent during respiratory infections.
- Macrolides may have a beneficial effect on the airway microbiome.

APRIL Trial (NHLBI AsthmaNet)

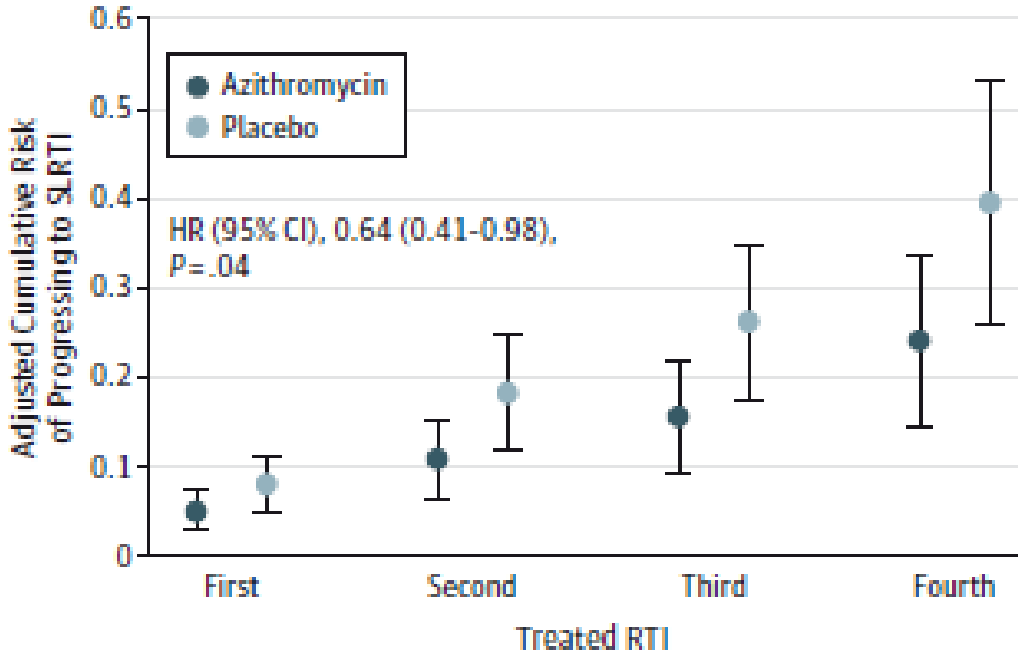
- 607 children (ages 1-5 years)
- Episodic wheeze events, but minimal day-to-day symptoms
- Multicenter, blinded, randomized, placebo controlled

- Azithromycin vs. Placebo
  - Parent-initiated at the start of an upper respiratory tract infection
  - 5 day course with each infection (12 mg/kg/day)
  - Children were not on any controller therapies

Bacharier LB, JAMA, 2015

Intermittent azithromycin reduced the risk of progression to severe wheezing exacerbations

Figure 2. Cumulative Risk of Experiencing an Episode of Severe LRTI Across Treated RTIs for Preschool Children With a History of Severe LRTI



No. of treated RTIs	223	220	146	147	78	74	26	23
No. of SLRTIs	16	22	13	19	5	9	1	7

Bacharier LB, JAMA, 2015

Summary of the APRIL Trial

- Intermittent early initiation of azithromycin was able to reduce the risk of an upper RTI progressing to a severe wheezing episode by 36% (similar to ICS effect) when compared to placebo.

- Additionally, the azithromycin group had significantly decreased illness severity during episodes that progressed to an exacerbation.

- There was no difference in the treatment effects between children with and without a positive mAPI (modified Asthma Predictive Index)
  - Suggesting that azithromycin may be a good option for children with a negative mAPI (often under-represented in asthma studies)

Bacharier LB, JAMA, 2015

Macrolides as treatment for asthma

- After the APRIL trial, similar beneficial results were reported from children aged 1-3 years in the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC)

- These studies indicate that intermittent azithromycin therapy may be a therapeutic approach for young children with recurrent and severe episodic wheeze.
  - Including those children with a negative mAPI

Bacharier LB, JAMA, 2015
Stockholm J, Lancet Respir Med, 2016

mAPI: modified Asthma Predictive Index

- Method for predicting asthma later in life
- In general, helps to identify young children with allergic-type asthma that will persist later in life
  - In contrast to infection-triggered wheezing that does not persist
- May help with personalized treatment approaches

Primary	≥ 4 wheezing episodes in a year		
AND			
Secondary	**Major (at least 1)**	**OR**	**Minor (at least 2)**
	Parental Asthma		Wheezing unrelated to colds
	Eczema		Eosinophils ≥ 4%
	Aeroallergen Sensitization		Food Allergen Sensitization

Let's try to put this all together

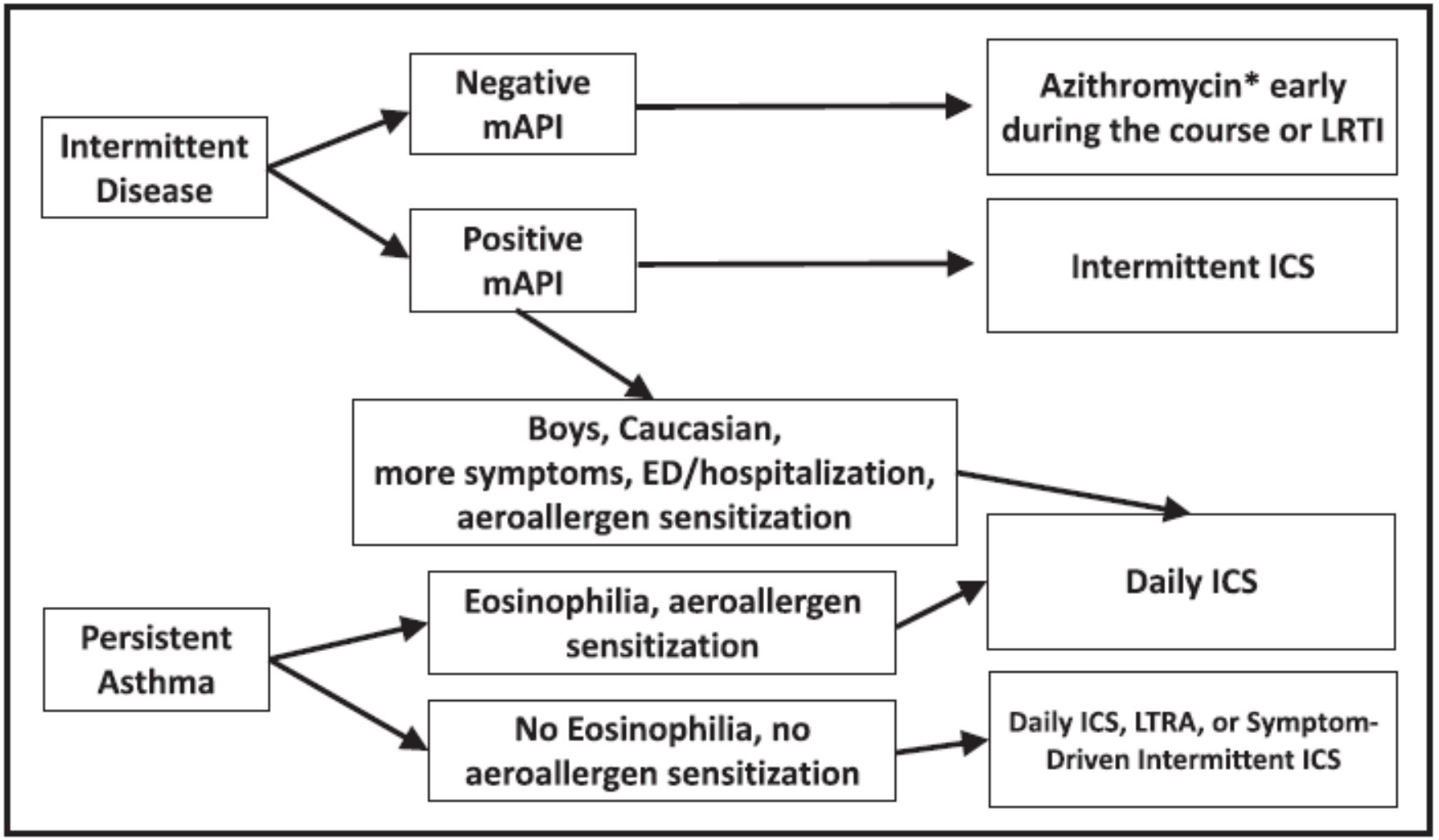
Personalized Medicine for Preschool Wheezers:

1. Disease Types:
   - Intermittent vs. Persistent

2. Predictive Factors:
   - mAPI, Eosinophilia, Aeroallergen Sensitization, Disease Burden

3. Treatments:
   - Daily ICS, Intermittent ICS, Montelukast (LTRA), Azithromycin

Personalized Medicine for Preschool Asthma



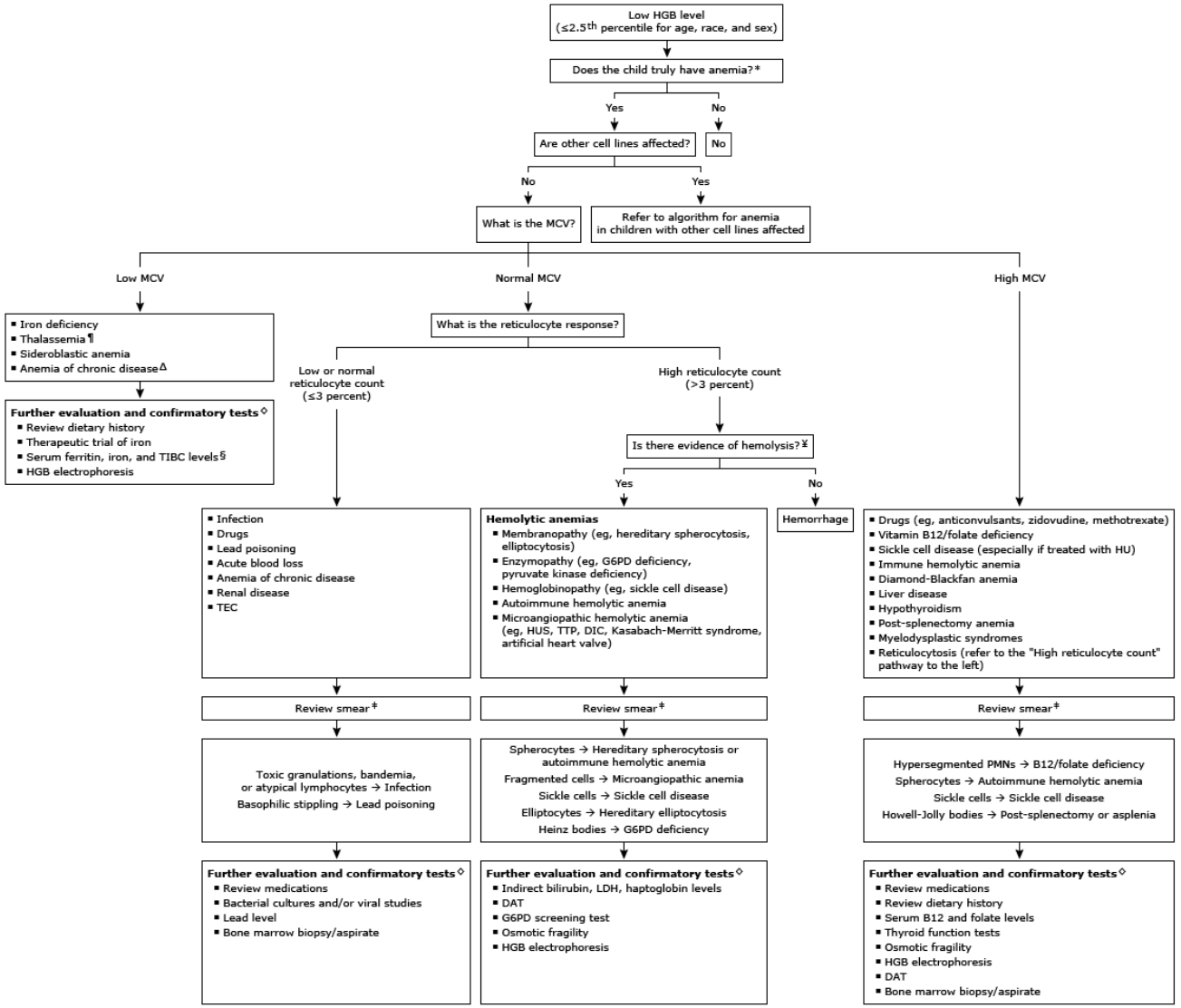
Beigelman A, Curr Opin Allergy Clin Immunol, 2017

Is this all too much?

- Maybe (at least for now)
  - That is why this is the “Future of Pediatrics” conference
- The “one size fits all” treatment of asthma is clearly not the best approach.
  - Such an approach would never be accepted in other diseases
  - Example: Anemia

Approach to Anemia in a Child

Diagnostic approach to isolated anemia in children: Morphologic classification

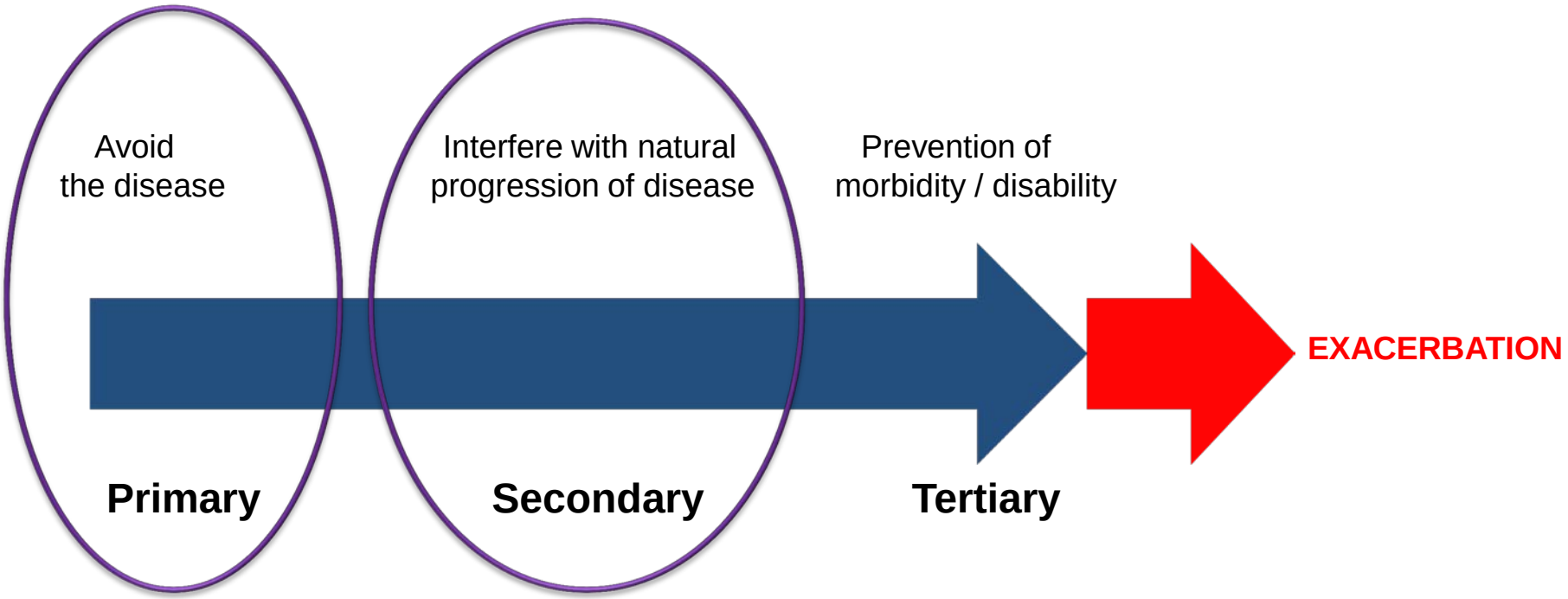


Future of Asthma Treatment: Specific Therapies

- “Asthma is heterogeneous, and there are many different forms of the disease. In fact, sometimes I tell audiences that, you know, until very late in the 19th century fever was considered a disease. The same will be said about asthma 20 or 30 or 50 years from now.”
  - Fernando Martinez, Lancet, 2006

PREVENTION ?

Can we prevent wheeze/asthma in these young children?



PARK Study (NIAID Multicenter Trial)
Preventing Asthma in high Risk Kids

- Enroll 250 children aged 2-3 years at high risk for the development of asthma
- Randomize to two years blinded treatment of:
  - Omalizumab (anti-IgE) vs. Placebo
- Two years of treatment followed by two years of observation
- Outcomes are assessed two years after stopping therapy
- Start enrolling in 2018, results in 2024-2025

NCT 02570984

ORBEX Study (NHLBI Multicenter Trial)

- **Or**al **B**acterial **Ex**tract for the Prevention of Wheezing Lower Respiratory Tract Illness
- Enroll 1,076 infants aged 6-17 months
- At risk for development of asthma, but not yet wheezing
  - Infant has Eczema or Family History of Asthma
- Randomize to two years blinded treatment of:
  - BronchoVaxom® (lyophilized bacterial extracts) vs. Placebo
- Primary outcome measured after stopping therapy
- **Children's National currently enrolling!**
  - If interested: 202-476-2628

Breathe Easy Early

An ORBEX Study of Asthma & Wheezing

NCT 02148796

Summary

- Wheezing in preschool children is the outward presentation of what is a diverse collection of pathophysiologic responses.

- Efforts to personalize treatments targeted for these different underlying processes could help to improve health outcomes in an efficient manner.

- Current research is underway to try to prevent wheezing in these children – and hopefully prevent asthma.

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