Paediatric Respiratory Updates

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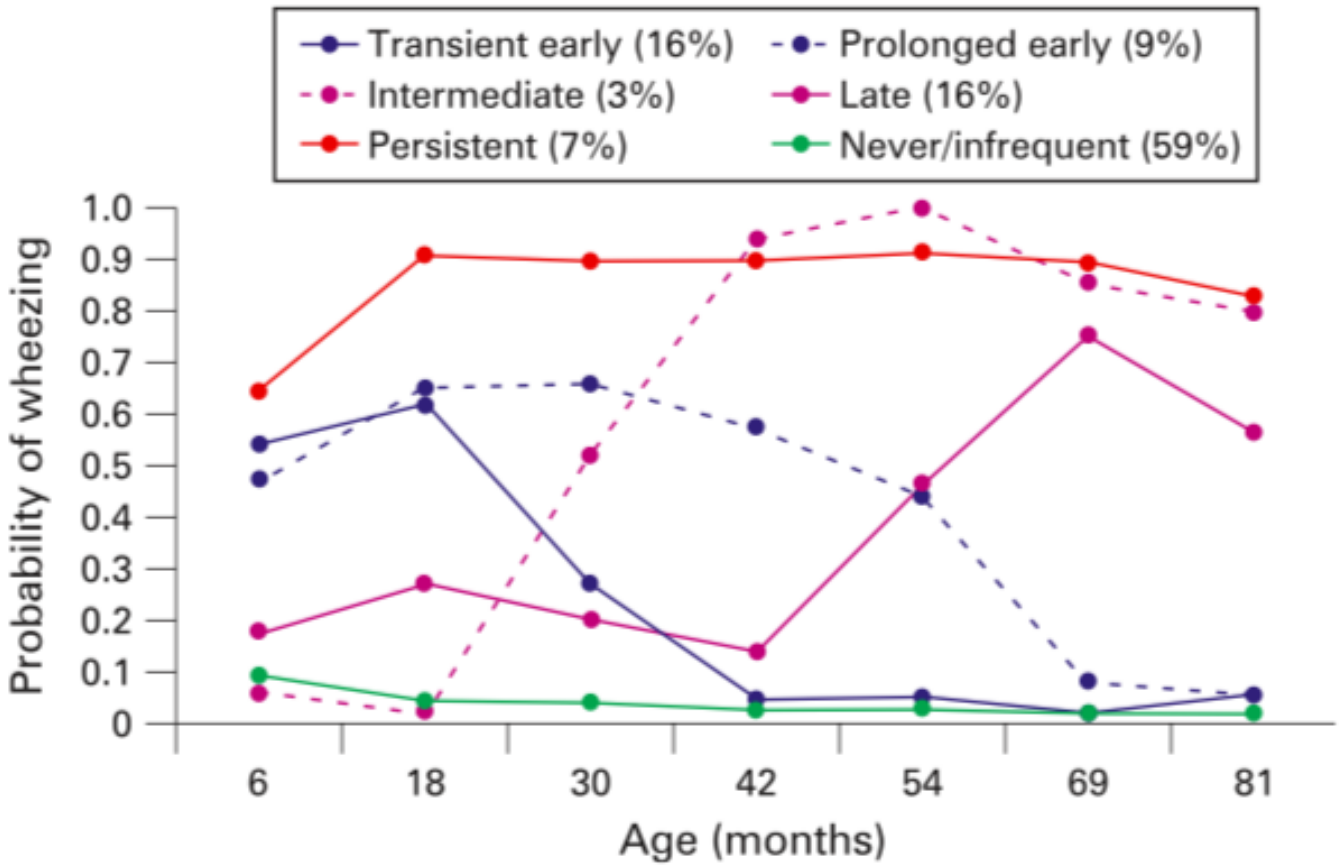

Figure 1 Estimated prevalence of wheezing at each time point from birth to 81 months for each of the six wheezing phenotypes identified by latent class analysis in 6265 children with complete data.

Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood

J Henderson,[1] R Granell,[2] J Heron,[2] A Sherriff,[2] A Simpson,[3] A Woodcock,[3] D P Strachan,[4] S O Shaheen,[5] J A C Sterne[2]

Phenotype	Physician-diagnosed asthma		Atopy (any skin prick sensitivity)	
	n/total (%)	OR (95% CI)	n/total (%)	OR (95% CI)
Transient early	79/931 (8.5%)	2.46 (1.48 to 4.09)	95/700 (13.6%)	0.8 (0.55 to 1.17)
Prolonged early	183/509 (36.0%)	14.87 (10.68 to 20.71)	57/383 (14.9%)	0.89 (0.58 to 1.38)
Intermediate	141/152 (92.8%)	325.75 (137.78 to 770.14)	71/114 (62.3%)	8.36 (5.24 to 13.36)
Late	260/341 (76.2%)	84.60 (56.00 to 127.8)	145/257 (56.4%)	6.62 (4.67 to 9.39)
Persistent	362/393 (92.1%)	307.93 (185.86 to 510.18)	123/296 (41.6%)	3.64 (2.76 to 4.81)
Never/infrequent	126/3397 (3.7%	1 (reference)	419/2554 (16.4%)	1 (reference)

- *Mean weal diameter ≥2 mm. CI, confidence interval; OR, odds ratio

Thorax 2008;**63**:974–980. doi:10.1136/thx.2007.093187

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

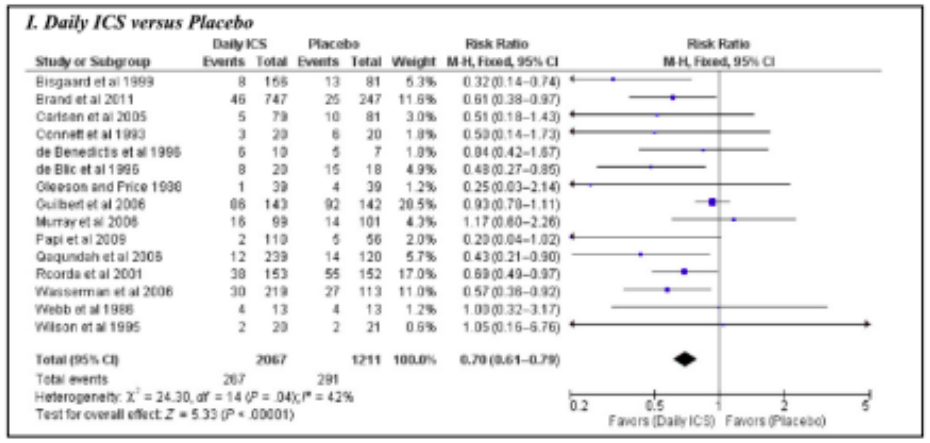
Sunitha V. Kaiser, Tram Huynh, Leonard B. Bacharier, Jennifer L. Rosenthal, Leigh Anne Bakel, Patricia C. Parkin and Michael D. Cabana

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

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

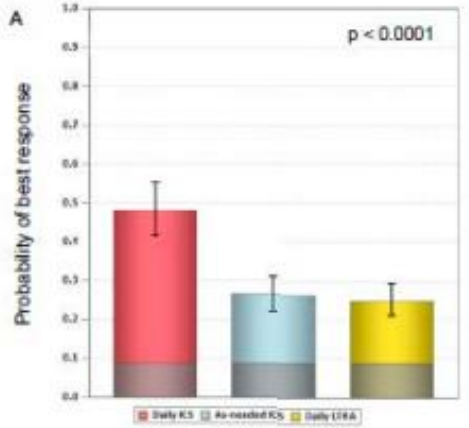
Daily ICS was most likely the preferred therapy when all children were combined

- 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

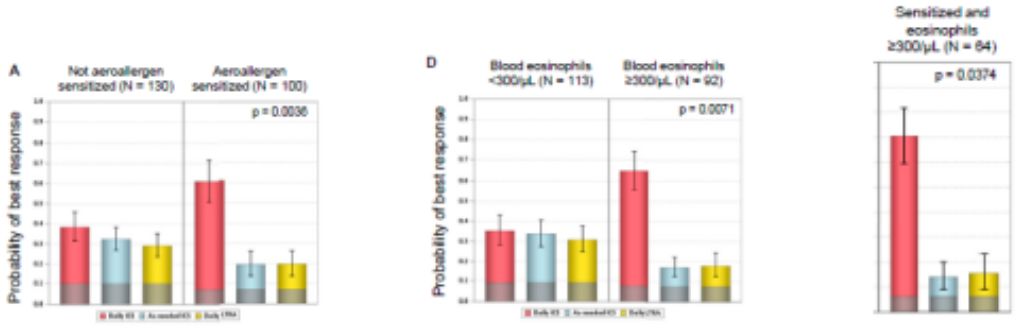
- 26% of children had no preferred choice (less severe)



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

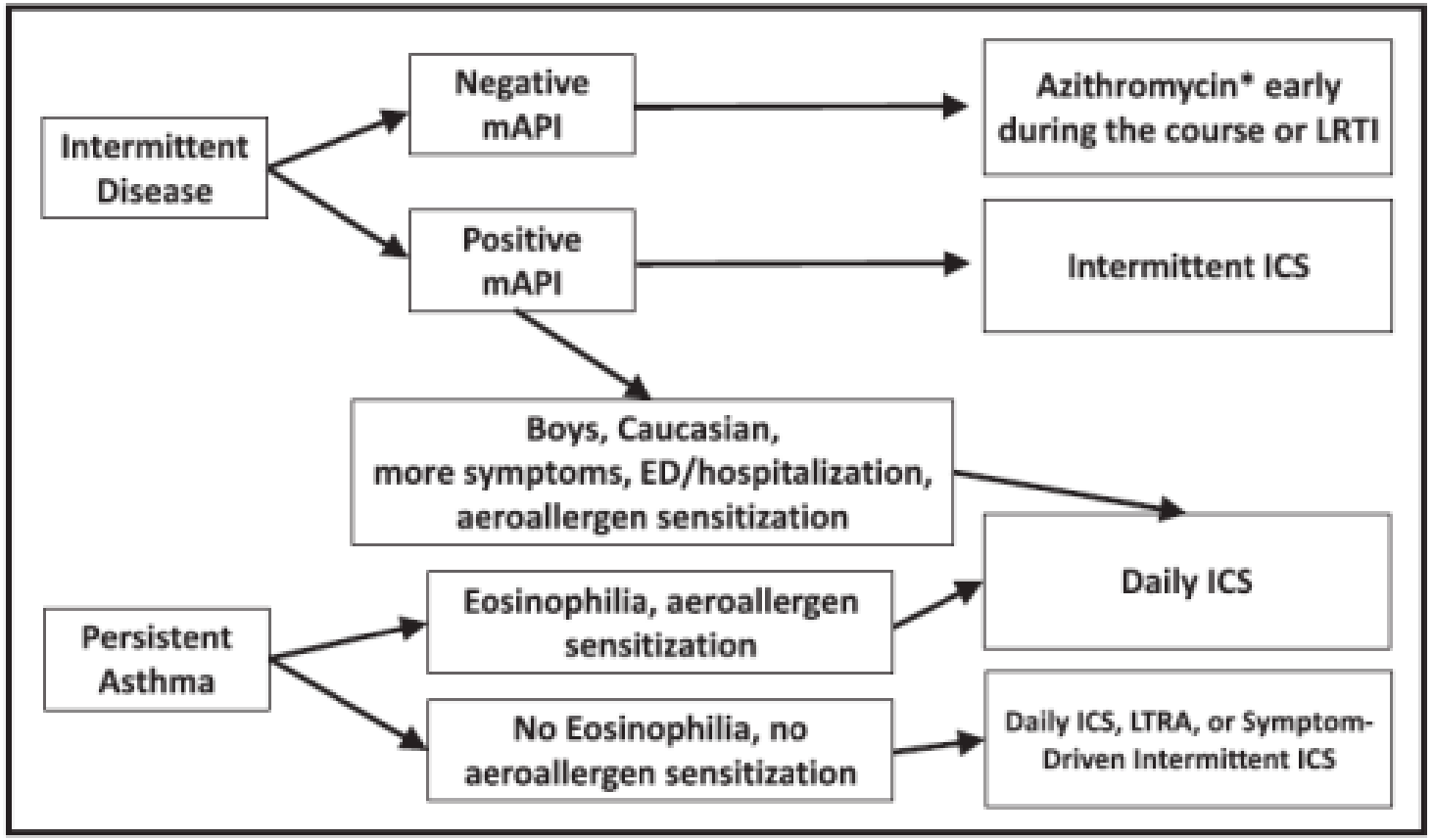
- ICS reduces the rate of exacerbations by approximately 30-40%, but does not completely prevent exacerbations.
- Daily ICS therapy has been associated with a small, but statistically significant, reduction in linear growth.
- Suboptimal adherence to Daily ICS is well documented.

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

Personalized Medicine for Preschool Asthma



Beigelman A, Curr Opin Allergy Clin Immunol, 2017

What's new in treatment of Mild Asthma?

- 50-70% of asthmatic patients suffer from mild asthma and up to 40% suffer exacerbations requiring emergency care[38].
- Frequent use of SABA increases airway hyperresponsiveness and is associated with a higher risk of fatal or near-fatal asthma[39].
- Dispensing of ≥3 canisters per year (average 1.7 puffs/day) is associated with higher risk of exacerbations[40].
- Global Initiative for Asthma (GINA) recommends regular, low-dose inhaled glucocorticoids as controller medication to reduce the risk of exacerbations and SABAs should be used as needed for symptom relief [38,41].

Anti-inflammatory therapy in Mild Asthma

- START study revealed that early ICS therapy in mild asthma[42]
  - significant decrease in exacerbations and use of oral steroids.
  - reduced decline in lung function and improved symptom control in patients across all subgroups [43].

- IMPACT study showed that continuous budesonide treatment [44]
  - significant improvement in symptom score and in number of symptom-free days
  - significantly reduces inflammation parameters - eosinophil concentration in sputum and exhaled nitric oxide levels.

- ICS are also known to provide a functional benefit to mild asthma patients and can alter asthma evolution in children by preventing bronchial remodelling [38].

Anti-Inflammatory reliever therapy - ICS / Formoterol in Mild Asthma

- The anti-inflammatory reliever therapy (AIR) with budesonide and formoterol is an on-demand symptom driven regimen with controller and reliever in the same single inhaler [45].
- Several studies such as SYGMA 1, 2, Novel START and PRACTICAL trials provide evidence of beneficial effects of anti-inflammatory reliever therapy in mild asthma [46,47,48,49].
  - Budesonide-formetorol used as needed was a more effective treatment than a SABA alone in patients with mild asthma for both symptom control and prevention of moderate to severe exacerbations
  - Budesonide-formetorol used as needed is inferior to budesonide maintenance for symptom control but exposes patient to (<1/4) of ICS dose

Assessment of Difficult Asthma

- Is the diagnosis correct?
- Is the drug delivery device appropriate?
- Are there important environmental issues?
- Are there important psychological issues i.e. Vocal Cord Dysfunction?

Difficult asthma

Difficult asthma is defined as persistent symptoms and/or frequent asthma attacks despite treatment with:

- high-dose ICS (adults) or medium-dose ICS (children) plus a LABA (age 5 and over) or LTRA; or
- medium-dose ICS (adults) or low-dose ICS (children) plus a LABA (age 5 and over) or LTRA and an appropriate additional therapy; or
- continuous or frequent use of oral steroid

Assessing difficult asthma

D	Patients with difficult asthma should be systematically evaluated, including: - confirmation of the diagnosis of asthma, and - identification of the mechanism of persisting symptoms and assessment of adherence to therapy.
D	This assessment should be facilitated through a dedicated multidisciplinary difficult asthma service, by a team experienced in the assessment and management of difficult asthma.

Factors contributing to difficult asthma

Poor adherence

C	Healthcare professionals should always consider poor adherence to maintenance therapy before escalating treatment in patients with difficult asthma.

Psychosocial factors

C	Healthcare professionals should be aware that difficult asthma is commonly associated with coexistent psychological morbidity.
D	Assessment of coexistent psychological morbidity should be performed as part of a difficult asthma assessment. In children this may include a psychosocial assessment of the family.
D	Dysfunctional breathing should be considered as part of the assessment of patients with difficult asthma.

Add-on biologic therapy for severe Type 2 asthma

- Additional indications for these therapies in Europe and/or USA have been listed
  - Omalizumab: chronic idiopathic urticaria, nasal polyposis
  - Mepolizumab: hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis (EGPA)
  - Benralizumab: no additional indications at present
  - Dupilumab: chronic rhinosinusitis with nasal polyposis (CRSwNP); atopic dermatitis
- Check local regulatory approvals and eligibility criteria

ICS: inhaled corticosteroids; LABA: long-acting beta$_2$-agonist

QUESTIONS?