Stepping-Up Care in Children with Severe Asthma

Jonathan Gaffin, MD, MMSc.
Co-Director, Severe Asthma Program
Co-Chair, Asthma Executive Committee
Division of Pulmonary Medicine
Boston Children's Hospital

Partners Asthma Center: Update on Severe Asthma 2023
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- Dr. Gaffin receives grant funding from NIH, Vertex, GSK
- Dr. Gaffin is a consultant to Syneos Health
  - Clinical trial endpoint adjudication

- Dr. Gaffin has no conflicts of interest related to this presentation

Objectives

- Review NAEPP EPR4 management changes affecting children with moderate - severe asthma, age 5-11years
- Review single maintenance and reliever therapy (SMART) approach to asthma care in children
  - Learn practical strategies for implementing SMART in clinic
- Discuss how to choose a biologic for children 6-11 years old

What changed in EPR4?

- December 2020, an expert panel from the National Asthma Education and Prevention Program published updates to the Asthma Management Guidelines
- First update since 2007
- The addition of Single Maintenance And Reliever Therapy was a Key management change for children 5 and older

- SMART has consistently been in European guidelines since 2013

Updates to 5–11-year-old step algorithm

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 5–11 Years				
Treatment	**STEP 1**	**STEP 2**	**STEP 3**	**STEP 4**	**STEP 5**	**STEP 6**
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily LTRA,* or Cromolyn,* or Nedocromil,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LTRA,* or daily low-dose ICS +Theophylline,* and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA or Daily medium-dose ICS + LTRA* or daily medium-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* or daily high-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* + oral systemic corticosteroid or daily high-dose ICS + Theophylline* + oral systemic corticosteroid, and PRN SABA
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider Omalizumab**▲	

Key Changes

- Initiate SMART therapy in **Step 3**
- Increase strength of SMART therapy in **Step 4**

Journal of Allergy and Clinical Immunology 2020 1461217-1270DOI: (10.1016/j.jaci.2020.10.003)

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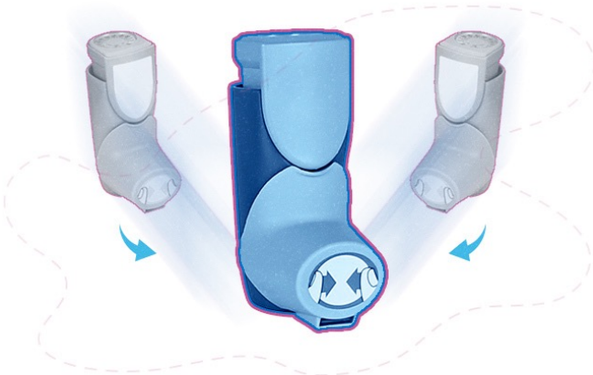
What is SMART?

- Use of a single combination inhaler to deliver ICS and fast acting LABA
- Only **Formoterol-**containing products (e.g. budesonide-formoterol (Symbicort) or mometasone-formoterol (Dulera)
- No use of SABA alone

➢ *Decreases inhaler confusion*

➢ *Minimizes SABA overuse*



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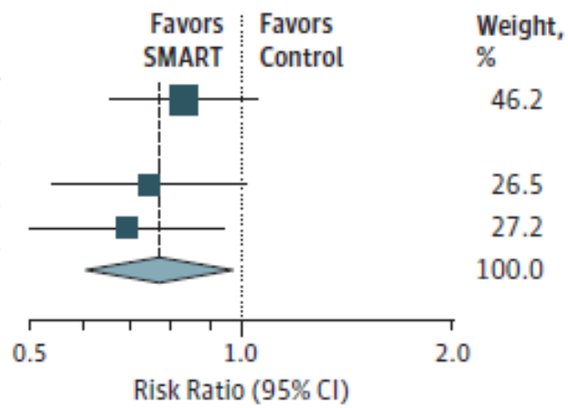
SMART improves exacerbation risk compared to *higher* dose ICS/LABA + SABA

Figure 3. Association of SMART With Exacerbations Requiring Systemic Corticosteroids, Hospitalization, or ED Visits Among Patients Aged 12 Years or Older vs a Higher Dose of Inhaled Corticosteroids and LABA Controller Therapy

Source	SMART Group		Control Group		Absolute Risk Difference (95% CI), %	Risk Ratio (95% CI)
	Total No. of Participants	No. With Event	Total No. of Participants	No. With Event		
Bousquet et al,[32] 2007	1151	108	1153	130	-2.7 (-5.2 to 0.6)	0.83 (0.65 to 1.06)
Kuna et al,[33] 2007						
Comparison 1	552	47	1099	126	-2.9 (-5.9 to 0.1)	0.74 (0.54 to 1.02)
Comparison 2	552	47	1119	138	-3.8 (-6.8 to -0.8)	0.69 (0.50 to 0.95)
Overall (random-effects model)	2254	202	3371	394	-2.7 (-5.2 to -0.3)	0.77 (0.60 to 0.98)

Heterogeneity: $I^2 = 0\%$, $P = .64$
Test for overall effect: $t_2 = -4.71$, $P = .04$



Sobieraj et al. JAMA 2018

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SMART improves risk of severe exacerbations compared to higher dose ICS or same dose ICS/LABA

Table 2. Summary of Findings and Strength of Evidence in Studies Comparing SMART vs Inhaled Corticosteroids With or Without a LABA as Controller Therapy Among Patients Aged 4 to 11 Years (n = 341)[a]

Outcome	Included Studies	SMART Group		Control Group[b]		Absolute Risk Difference (95% CI), %[c]	Risk Ratio (95% CI)	Strength of Evidence[d]
		No. of Patients	No. With Event	No. of Patients	No. With Event			
SMART vs Higher Dose of Inhaled Corticosteroids as Controller Therapy								
Asthma exacerbations								
Required use of systemic corticosteroids, hospitalization, ED visit, increase in inhaled corticosteroids or other asthma medication, or having PEF <70%	31	118	17	106	28	−12.0 (−22.5 to −1.5)	0.55 (0.32 to 0.94)	Low
Required use of systemic corticosteroids, hospitalization, ED visit, or increase in inhaled corticosteroid or other asthma medication	31	118	10	106	21	−11.3 (−20.7 to −2.2)	0.43 (0.21 to 0.87)	Low
Mild	31	118	74	106	77	−9.9 (−21.7 to 2.4)	0.86 (0.72 to 1.04)	Low
SMART vs Same Dose of Inhaled Corticosteroids and LABA as Controller Therapy								
Asthma exacerbations								
Required use of systemic corticosteroids, hospitalization, ED visit, increase in inhaled corticosteroids or other asthma medication, or having PEF <70%	31	118	17	117	44	−23.2 (−33.6 to −12.1)	0.38 (0.23 to 0.63)	Low
Required use of systemic corticosteroids, hospitalization, ED visit, or increase in inhaled corticosteroid or other asthma medication	31	118	10	117	36	−22.3 (−31.9 to −12.3)	0.28 (0.14 to 0.53)	Low
Mild	31	118	74	117	98	−21.1 (−31.6 to −9.8)	0.75 (0.64 to 0.88)	Low

Abbreviations: ED, emergency department; LABA, long-acting β-agonist; PEF, peak expiratory flow; SMART, single maintenance and reliever therapy.

[a] The median age of patients was 8 (range, 4-11) years and 69 (31%) were female.

[b] The control group used a short-acting β-agonist as the reliever therapy.

[c] Indicates between-group risk (SMART group minus control group).

[d] Based on domains of risk of bias, consistency, directness, precision, and publication bias. Additional information appears in eAppendix 2 in the Supplement.

Sobieraj et al. *JAMA* 2018

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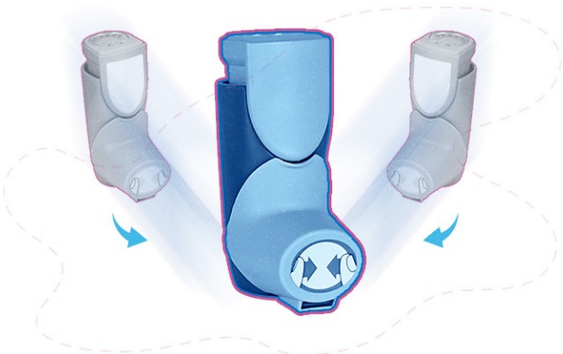
SMART *in practice*

- Prescribed as single inhaler for all situations
  - **Must use FORMOTEROL** – containing drug
  - Well dosing: 1-2 puffs, 1-2 times per day
  - Rescue dosing: 1-2 puffs as needed
  - Maximum daily puffs (4-11yrs): 8
- Ok to use back-to-back in Red Zone AAP
  - Up to 4 puffs (4-11y) recommended at a single occasion



Examples of SMART meds age 4-11 years		
Step 3	Budesonide-formoterol (Symbicort) 80mcg, 1 puff daily + 1 puff PRN	Mometasone-formoterol (Dulera) 50mcg, 2 puff BID + 1 puff PRN
Step 4	Budesonide-formoterol (Symbicort) 80mcg, 1 puff BID + 1 puff PRN	Mometasone-formoterol (Dulera) 100mcg, 2 puff BID + 1 puff PRN
Notes: titrate to lowest effective maintenance dose; Maximum ICS-formoterol dose = 8 puffs/24hrs; Mometasone not formally studied for SMART use.		

Reddel HK et al. JACI in Practice. 2022

in practice: Poorly controlled asthma vignette

- Albert is a 10 year-old boy with moderate persistent asthma who presents for follow-up asthma visit
  - Was seen last week for a prednisone burst for URI induced exacerbation (3rd course of prednisone/12 months)
  - Triggers include springtime allergies
    - Uses albuterol 2-3 times/week during spring allergy season
    - Exercise is sometimes a problem during allergy season
  - Prescribed Fluticasone-salmeterol 110mcg, 2 puffs BID + Albuterol q4hr PRN
  - Reports he forgets to use controller 3-4 times/week

- Examination notable for mild nasal turbinate edema; clear lungs

What to do about Albert?

- Step up options:
  - Daily and PRN medium dose ICS/formoterol (SMART therapy)
  - Daily medium dose ICS/LABA + albuterol PRN
  - Daily high dose ICS + albuterol PRN
  - Daily medium dose ICS, daily montelukast + albuterol PRN
- Considerations in favor of SMART
  - Lower daily ICS dose
  - Only needs 1 inhaler
  - Concern about inadequate adherence – now always gets ICS when ill, at least
- Considerations against SMART
  - Effort to get insurance approval
  - Patient/family preference
  - Lack of FDA approval

Alberts new AAP

- Green zone:
  - Budesonide-formoterol 80mcg,1puff twice a day
- Yellow zone
  - Budesonide-formoterol 80mcg,1puff as needed for cough, wheeze or shortness of breath, not to exceed 8 puffs/day
- Red zone
  - Budesonide-formoterol 80mcg, 1 puff, may repeat every 20 minutes x 3
  - Seek medical attention

Note: no time interval (i.e. not q4hrs)

As needed ICS/SABA?

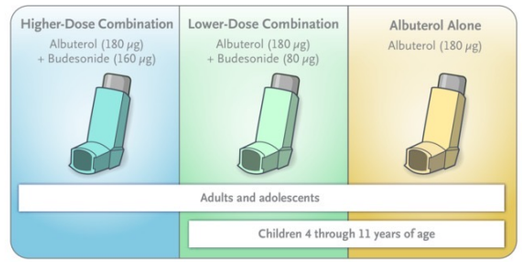
The NEW ENGLAND JOURNAL of MEDICINE

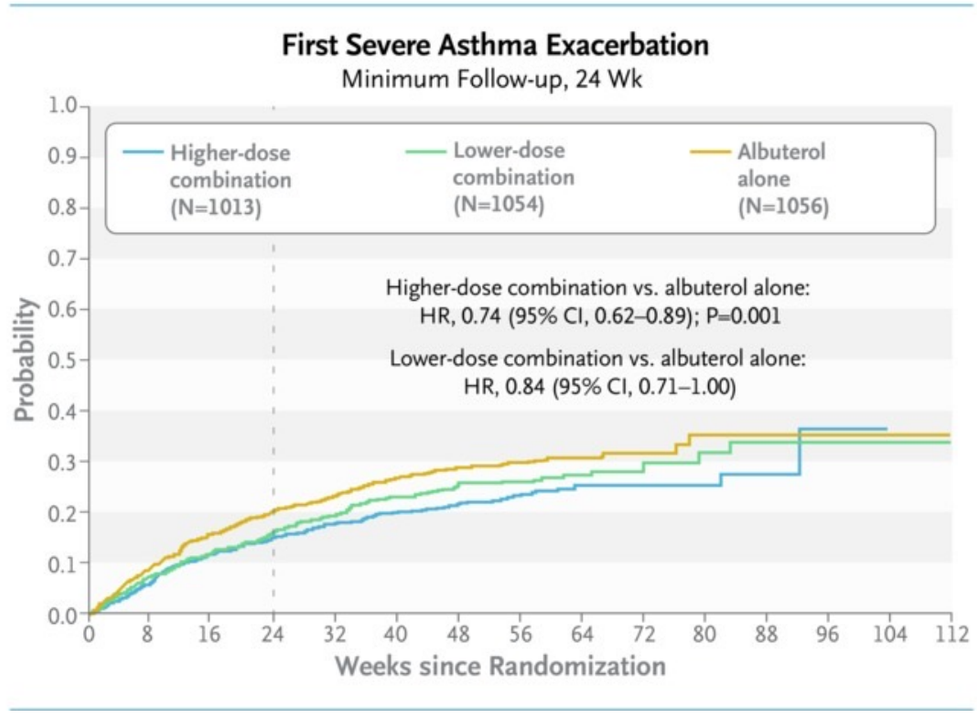
RESEARCH SUMMARY

Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Papi A et al. DOI: 10.1056/NEJMoa2203163

- Randomized controlled trial.
- Setting 295 sites across North and South America, Europe and South Africa.
- Participants: Children (aged 4 years and over) and adults with asthma requiring maintenance ICS and with a history of at least one severe exacerbation in the preceding 12 months. Participants had to have evidence of inadequate asthma control at screening but did not use oral steroids or biological agents in the three months prior to screening.
- Intervention: 180 mg of albuterol and 160 mg of budesonide, 180 mg of albuterol and 80 mg of budesonide or 180 mg of albuterol alone. (Children aged 4 to 11 years were not randomized to higher-dose ICS).
- Main Results: Time to exacerbation analysis- the risk of severe exacerbation was lower only in the group receiving the higher dose (160 mg) of ICS compared with the albuterol-alone group, hazard ratio 0.74 (95% CI, 0.62-0.89).
- Pediatric applicability: unknown.
  - < 3% of the cohort was under 12 years, none treated with efficacious regimen
  - only 100 12-17 year olds



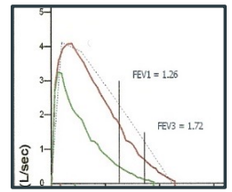


Selecting A Biologic Agent
Children 6-11 years old

Vignette

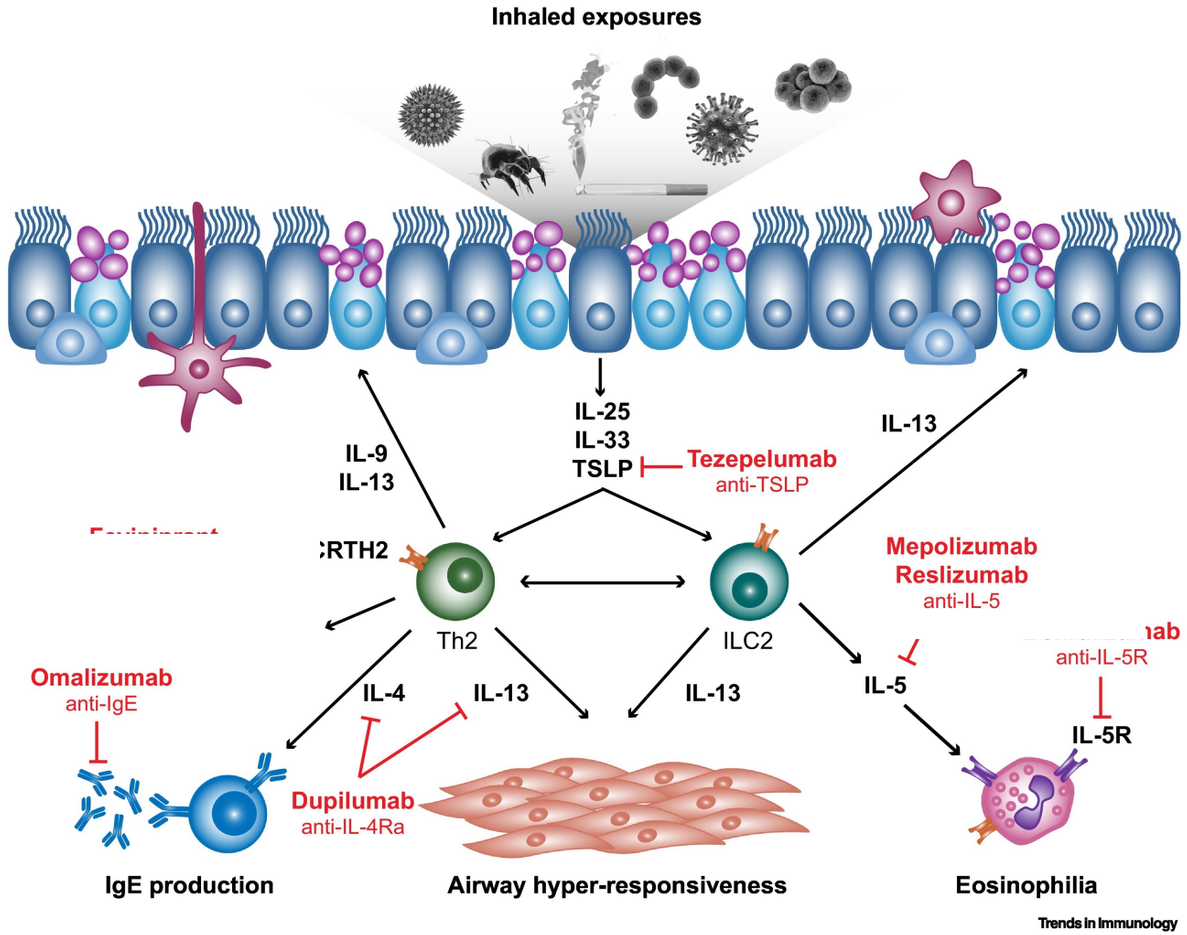
Kimberly

- 10-year-old girl referred for difficult-to-control asthma with frequent exacerbations
  - Full term delivery, asthma dx age 3 years
  - Increased exacerbation severity and frequency over past 2 years
  - Risk: 8 exacerbations in past year (5 ED visits, 3 inpatient, 1 ICU (CPAP))
  - Impairment: occasional exertional symptoms, particularly in spring
  - Comorbid conditions: Atopic dermatitis (severe); Allergic rhinitis; food allergies (peanut/treenut), significant anxiety
  - Adherence/technique: good
- Pertinent examination findings
  - Normal vital signs
  - Clear oropharynx and nasal passages
  - Clear chest examination
- Data
  - Spirometry: FVC: 113pp, FEV1 93pp BDR 16%; normal inspiratory loop
  - FeNO: 21 (on ICS)
  - Ige: 1094, SPT + HDM, trees and grasses
  - Absolute eosinophil count: 460 cells/uL



- Initial interventions
  - Referred to psychology, started SSRI
  - Home visit arranged
  - Continued bud-form 160 2puffs BID, Montelukast 5mg, added Tiotropium 2.5mg qd
- Outcomes
  - Able to differentiate anxiety from asthma; improved anxiety sx
  - Continued to have 3 exacerbations over next six months
  - **Decided to start biologic**

Monoclonal Antibodies in Pediatric Asthma



Lloyd CM et al. Trends in Immunology 2019

Clinical decision-making

For whom do we consider biologics?

- Uncontrolled asthma on high dose ICS or OCS
- Severe asthma requiring high dose ICS or OCS
- Side effects from ICS
  - Adrenal insufficiency
  - Behavioral issues with ICS (rare)
  - Poor growth

Type 2 inflammation

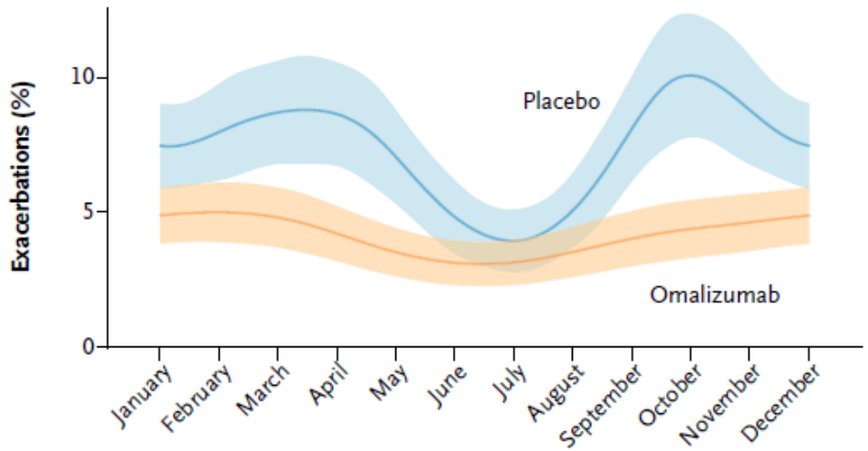
- Blood Eosinophils ≥ 150 *and/or*
- Allergy driven symptoms *and/or*
- FeNO ≥ 20 ppb *and/or*
  - (Sputum Eosinophils ≥ 2% *and/or)*
- Need for maintenance OCS

FDA approved biologics for asthma, age 6-11 years

Drug name	Omalizumab	Mepolizumab	Dupilumab
Brand name (manufacturer)	Xolair (Genentech/Novartis)	Nucala (GlaxoSmithKline)	Dupixent (Sanofi/Regeneron)
Age range	6 years and older	6 years and older	6 years and older
# Children in asthma registry studies	926 (6- ≤12 y.o.) +Many non registry	36 (6 - ≤12 y.o.) 290 non-registry	405 (6- ≤12 y.o.)
Indication	Moderate to severe asthma with perennial aeroallergen sensitization	Severe asthma with an eosinophilic phenotype	Moderate-to-severe asthma with an eosinophilic phenotype or OCS-dependent asthma
Biomarker cutoffs	IgE level 30-1300 IU/mL, allergen sensitization	No strict EOS cutoff but generally ≥150-300 cell/μL used	No strict EOS cutoff but generally ≥150-300 cell/μL used
Other FDA indication(s)	Chronic Idiopathic Urticaria (≥12 y.o.), Nasal Polyps (adult)	HES (≥12 y.o.), CRSwNP, EGPA (adult)	AD (≥6 y.o.), CRSwNP (adult), EoE (≥ 12 y.o.)
Mechanism of action	Binds to IgE	Binds to IL-5	Binds IL-4Rα, inhibits IL-4 & IL-13 signaling
Frequency	every 2 or 4 weeks	every 4 weeks	every 2 weeks
Location	office or home	office or home	office or home

Anti-IgE: Omalizumab

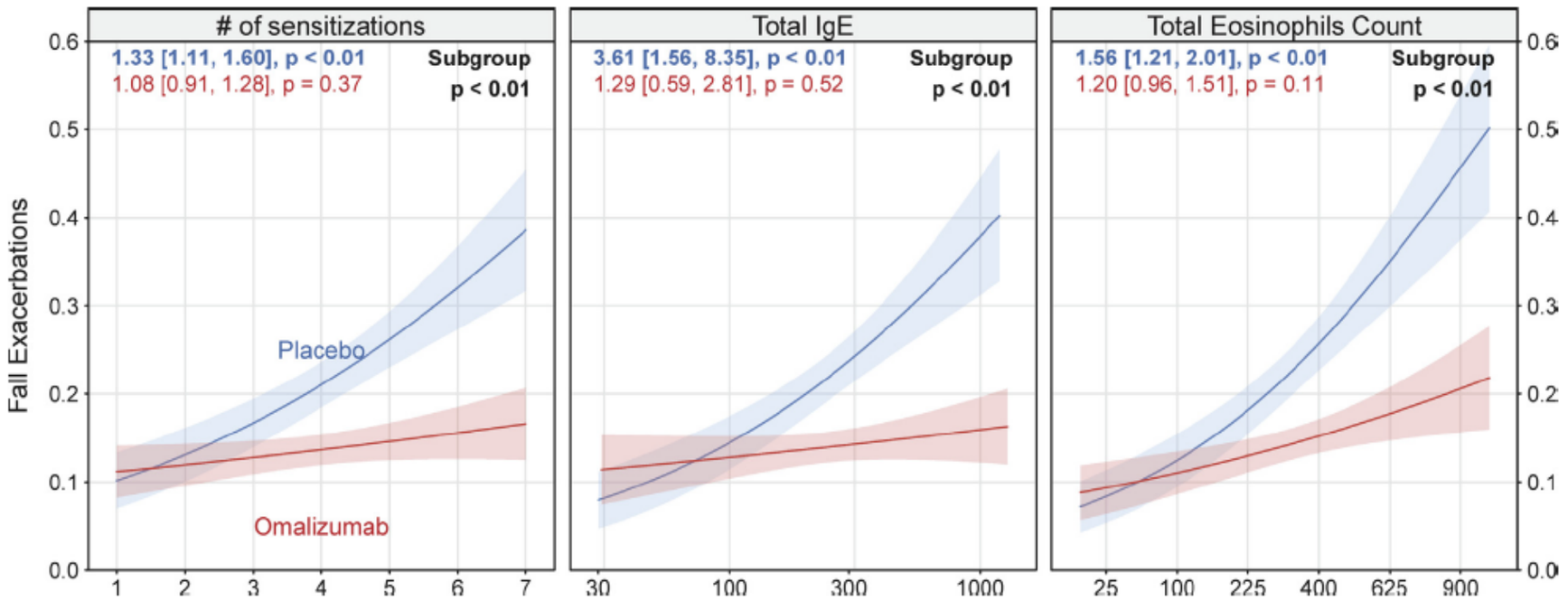
- Indications:
  - Age ≥ 6 years
  - IgE 30 – 1300 (6 – 12 years)
  - Perennial sensitization
  - (Chronic urticaria, CRSwNP)
- Predictive biomarker
  - FeNO > 20
  - Blood eos ≥ 260/μL
- Outcomes
  ~ 45% decreased exacerbation
  - Dose reduction of ICS
  - Small Improvement in symptoms
  - Minimal effect on FEV1
- Adverse effects
  - Anaphylaxis (up to 0.2%)
  - Malignancy - *Not* associated in post-marketing safety study



Busse WW, et al. (2011) NEJM

Pillai P, et al. (2016) ERJ
Garcia G, et al. (2013) CHEST
Long A, et al. (2014) JACI

Aeroallergen sensitization, total IgE, and total eosinophil count predicted differential response to omalizumab

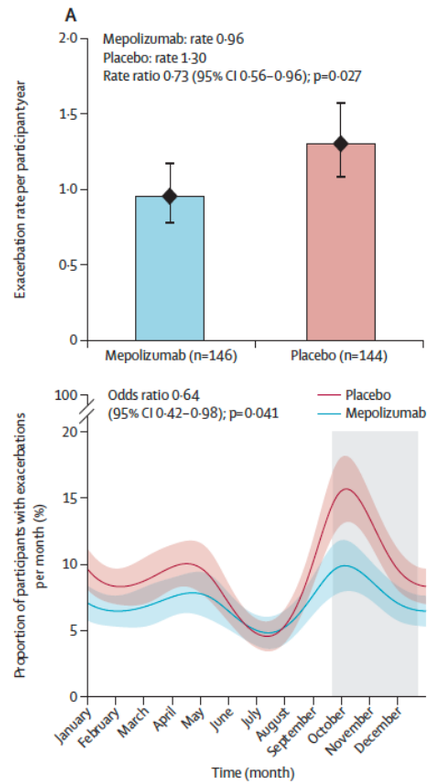


Sheehan WJ et al. JACI IP, 2020

Anti-IL-5: Mepolizumab

- Indications:
  - Age ≥ 6 years
  - Blood Eos >150 current or >300 in past 12 mos
  - (HES (≥12 y.o.), CRSwNP, EGPA (adult))
- Predictive biomarker
  - Blood eosinophils
  - Number of exacerbations
- Outcomes

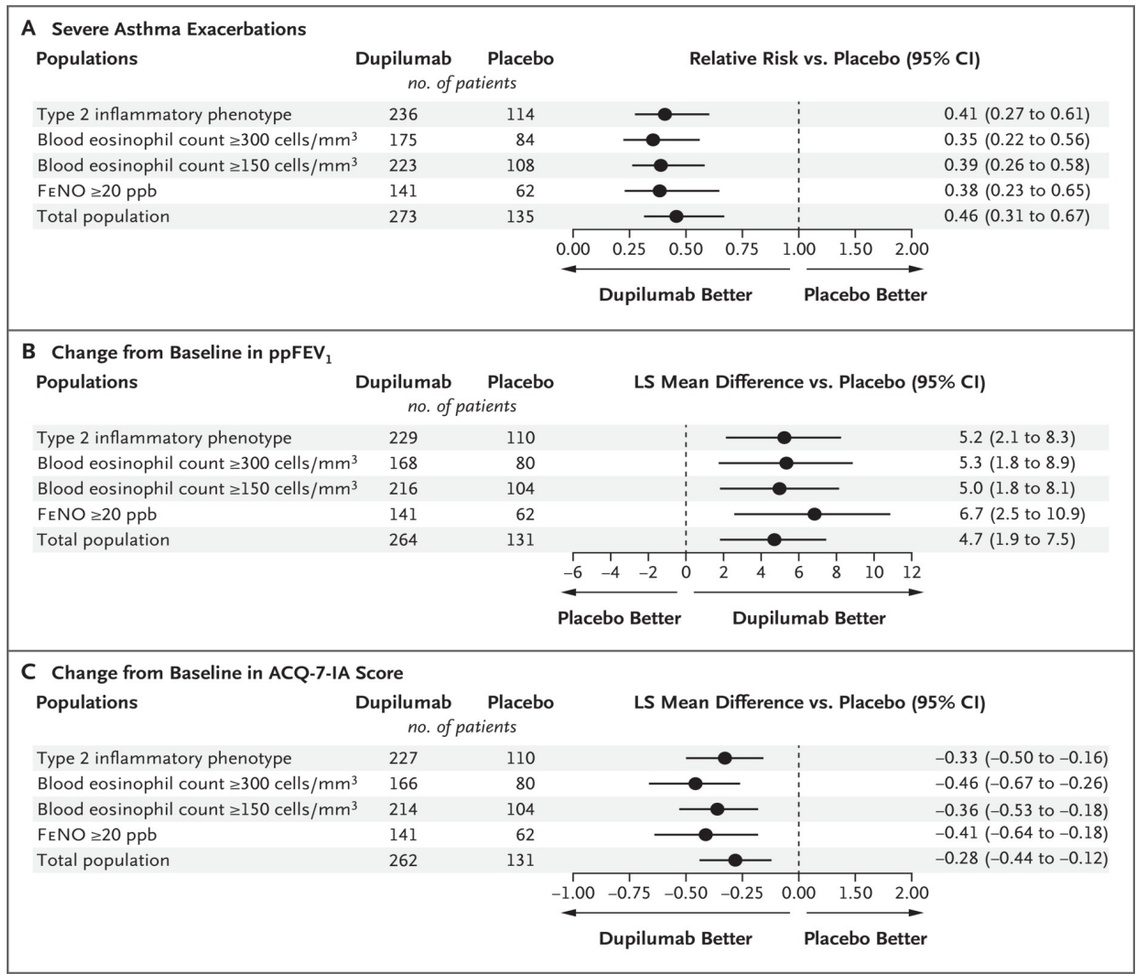
  ~ 27 - 47% decreased exacerbation
  (correlation with eosinophil level and # exacerbations)
  - Dose reduction of OCS
  - ↑symptom scores
  - Modest↑ FEV1 (adult)
- Adverse effects
  - Herpes zoster
  - **Anaphylaxis (recently added)**



Jackson DJ, et al.Lancet. 2022

Anti-IL4r: Dupilumab

- Indications
  - Age ≥ 6 years
  - Moderate-severe asthma
  - Eosinophilia or OCS dependent
  - (Atopic Dermatitis, CRSwNP)
- Predictive biomarkers
  - Blood eosinophils
  - FeNO
- Key Outcomes
  - ↓ exacerbations (47 - 65%)
  - Moderate ↑ on FEV1 (150mL)
  - ↓ OCS
- Adverse effects
  - Transient ↑ blood eosinophils
  - Ocular inflammation (atopic dermatitis)



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Bacharier LB et al. N Engl J Med 2021;385:2230-2240
Rabe KF et al. N Engl J Med 2018; 378: 2475-2485

Summary of effectiveness by domain for pediatric use

Drug name	Omalizumab	Mepolizumab*	Dupilumab
Exacerbation Rate	~↓ 25 - 50%	~↓ 50%	~ ↓ 50%; (↓65% w/eos>300)
FEV1	+/-	+/-	+ (++ w/eos>300)
Symptoms	+	+	+/-
Steroid wean*	+	++	++

*pediatric outcomes extrapolated from adolescent-adult data

- No head-to-head comparative efficacy studies
- Consistent benefit in exacerbation reduction

Overview of AE Profiles of Approved Biologics

Omalizumab	Arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, earache **Black box warning: anaphylaxis**
Mepolizumab	Headache, injection-site reaction, back pain, fatigue; helminth infection, zoster
Dupilumab	Injection-site reactions, oropharyngeal pain, eosinophilia, conjunctivitis, blepharitis, oral herpes, keratitis; helminth infection

*Data are from unrelated studies

Biomarkers driving treatment decision

Lab Evaluation

- Specific Aeroallergen Sensitization (ss-IgE or SPT) → **First**
- CBC with diff (absolute eosinophil count) → **Second**
- Total IgE

Respiratory Measures

- FeNO → **Third**
- Spirometry

Clinical History

- Symptom frequency
- Severe exacerbation history

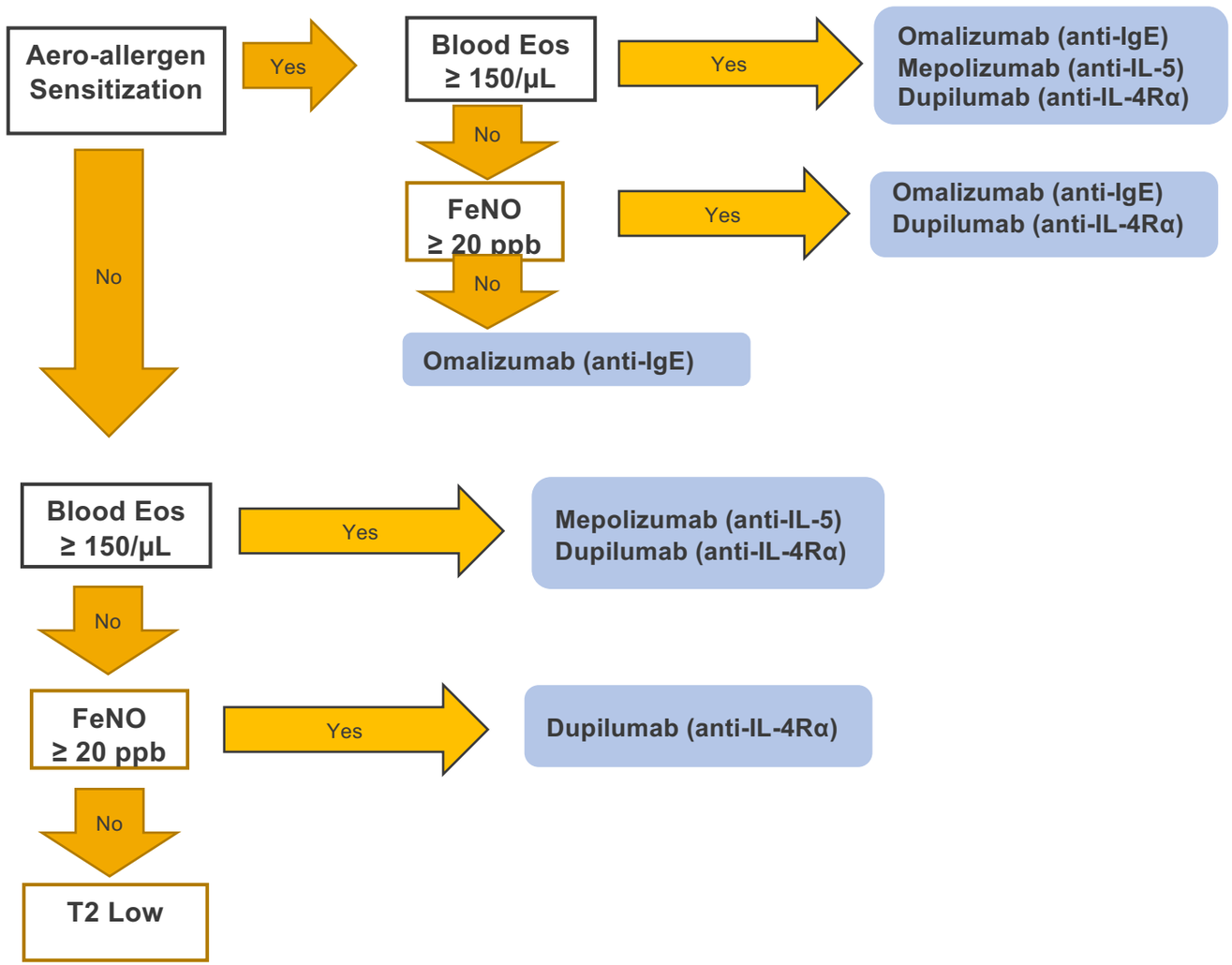
Comorbid conditions

- Eczema? Chronic Urticaria? Nasal Polyps? EoE?

Adherence !

Choosing a biologic, age 6-11 years

Utilizing predictive biomarkers



Additional considerations

- Concurrent T2 condition?
  - Atopic dermatitis → Dupilumab
  - Chronic idiopathic urticaria → Omalizumab
  - Chronic rhinosinusitis with nasal polyps → any
- Patient preferences
  - Length of approval
  - Dosing schedule
  - Clinic versus home administration
  - # injections/Needle phobia/trauma
- Side effect profile

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Strategies for Shared Decision-Making in the Management of Severe Asthma

- Before starting treatment: ask patients and caregivers about their goals for treatment and preferences for choice of medication (eg, a conventional vs a novel agent), dosing frequency, and home- vs office-based administration
- Once treatment has been started, ask patients and caregivers about their satisfaction with treatment
- Review response to add-on biologic therapy after 3 to 4 months, and every 3 to 6 months for ongoing care
- In case of inadequate response, review factors contributing to symptoms, exacerbations and poor quality of life

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Summary – Stepping-Up Care in Children with Severe Asthma, age 5-11 years

- NAEPP EPR4 guidelines introduce SMART management in Steps 3 and 4
  - Benefits include lower total ICS exposure for improved exacerbation outcomes
- Several biologic agents are available for add on therapy for allergic or eosinophilic asthma
  - All decrease exacerbation rate
  - Variable improvement in FEV1
- A combination of biomarker-driven selection and patient and family-centered shared decision-making is necessary to identify the best drug for the patient

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