

A case-based presentation to highlight newest recommendations in treatment of mild asthma

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Disclosures/Conflict of interest

- Dr. Kopel: Advisory board moderator, Covis Pharma Canada Ltd, Oct 2020
- Sophie Vallee-Smejda: None
- We do not currently have an affiliation (financial or otherwise) with a commercial entity

Objectives

- Review Canadian Thoracic Society (CTS) 2021 asthma guidelines (focus on pediatrics)
 - Review evidence behind the main changes
- Review commonly used classes of asthma medications
- Develop a strategy to step up therapy for pediatric patients with poor asthma control
- Review some once daily inhaler options

RESPIRATORY MEDICATIONS



RELIEVERS		SABA		Strength	Capacity
Airomir®**†	(salbutamol) Valeant	100mcg	200 actuations/canister, 100 actuations for hospital pack		
Bricanyl® Turbuhaler®**†	(terbutaline) AstraZeneca	0.5mg	100 or 200 doses/device		
Ventolin® HFA **††	(salbutamol) GlaxoSmithKline	100mcg	200 actuations/canister		
Ventolin® Diskus®**††	(salbutamol) GlaxoSmithKline	200mcg	60 blisters/device		
Salbutamol HFA generic products such as: Apo-Salvent® Apotex, Salbutamol HFA Sanis, Novo-Salbutamol HFA Teva					
Short-Acting Muscarinic Antagonist (SAMA) (Anticholinergic)					
Atrovent® HFA††	(ipratropium) Boehringer Ingelheim	20mcg	200 actuations/canister		
CONTROLLERS/MAINTENANCE		ICS		Strength	Capacity
Aermony Respiclick**	(fluticasone propionate) Teva	BID	55mcg, 113mcg, 232mcg	60 actuations/device	
Alvesco®†	(ciclesonide) AstraZeneca	OD or BID	100mcg, 200mcg	120 actuations/canister	
Amuity™ Ellipta®*	(fluticasone furoate) GlaxoSmithKline	OD	100mcg, 200mcg	14 or 30 blisters/device	
Asmanex® Twisthaler®*	(mometasone) Merck	OD or BID	100mcg, 200mcg, 400mcg	30 (100 & 400mcg) or 60 (200 & 400mcg) doses/device	
Flovent® Diskus®*	(fluticasone propionate) GlaxoSmithKline	BID	100mcg, 250mcg, 500mcg	60 blisters/device	
Flovent® HFA††	(fluticasone propionate) GlaxoSmithKline	BID	50mcg, 125mcg, 250mcg	120 actuations/canister	
Pulmicort® Turbuhaler®*	(budesonide) AstraZeneca	BID	100mcg, 200mcg, 400mcg	200 doses/device	
Ovar™††	(beclomethasone) Valeant	BID	50mcg, 100mcg	200 actuations/canister	
CONTROLLERS/MAINTENANCE		LABA		Strength	Capacity
Long-Acting Bronchodilators also known as: Long-Acting Beta2-Agonist (LABA)					
Foradil®**†† via Aerolizer®	(formoterol) Novartis	BID	12mcg	60 capsules/carton	
Onbrez® Breezhaler®†	(indacaterol) Novartis	BID	75mcg	10 or 30 capsules/carton	
Oxeze® Turbuhaler®*	(formoterol) AstraZeneca	BID	6mcg, 12mcg	60 doses/device	
Serevent® Diskus®**††	(salmeterol) GlaxoSmithKline	BID	50mcg	60 blisters/device	
CONTROLLERS/MAINTENANCE		ICS-LABA combinations		Strength	Capacity
Advair®*†	(fluticasone propionate/salmeterol) GlaxoSmithKline	BID	125/25mcg, 250/25mcg	120 actuations/canister	
Advair® Diskus®**††	(fluticasone propionate/salmeterol) GlaxoSmithKline	BID	100/50mcg, 250/50mcg, 500/50mcg	28 or 60 blisters/device	
Atractura® Breezhaler®†	(indacaterol acetate/mometasone furoate) Novartis	OD	150/80mcg, 150/150mcg, 150/320mcg	30 capsules/carton	
Breo® Ellipta®**††	(fluticasone furoate/vilanterol) GlaxoSmithKline	OD	100/25mcg**††, 200/25mcg**††	14 or 30 blisters/device	
Symbicort® Turbuhaler®**††	(budesonide/formoterol) AstraZeneca	OD or BID	100/6 mcg, 200/6mcg (FORTE)	120 doses/device	
Wixela® Inhub®**††	(fluticasone propionate/salmeterol) Mylan Inc.	BID	100/50mcg, 250/50mcg, 500/50mcg	60 blisters/device	
Zenhale®†	(mometasone/formoterol) Merck	BID	100/5mcg, 200/5mcg	120 actuations/canister	
Other Fluticasone/salmeterol products: pms-Fluticasone propionate/Salmeterol DPI					

<https://cts-sct.ca/guideline-library/>

Topic	Title	Date	Status	Evidence Profile
Asthma	2021 Guideline update: Diagnosis and management of asthma in preschoolers, children and adults	August 2021 - correction note Dec 2021	Current	
Asthma	2021 Canadian Thoracic Society Guideline – A Focused Update on the Management of Very Mild and Mild Asthma	February 2021	Current	GRACE Evidence Profiles - Very Mild and Mild Asthma
Asthma	Addressing therapeutic questions to help Canadian physicians optimize asthma management for their patients during the Covid-19 pandemic - Position statement	April 2020	Current	
Asthma	Recognition and management of severe asthma - Position Statement	2017	Current	
Asthma	Diagnosis & management of asthma in preschoolers - Position Statement	2015	Under Review	
Asthma	Guideline: CTS 2012 guideline update: Diagnosis and management of asthma in preschoolers, children and adults	2012	Under Review	
Asthma	Asthma Management Continuum – Consensus Summary for children six years of age and over, and adults	2010	Under Review	
Asthma	Guideline: Summary of Recommendations from the Canadian Asthma Consensus	2003	Archived	
Asthma	Adult Asthma Consensus Guidelines Update	2003	Archived	
Asthma	2003 Guideline: Canadian Pediatric Asthma Consensus	2005	Archived	
Asthma	Canadian Asthma Consensus Report	1999	Archived	
Asthma	Guideline for Occupational Asthma	1998	Archived	

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Canadian Thoracic Society 2021 Guideline update: Diagnosis and management of asthma in preschoolers, children and adults

Case 1: Wayne

- 14-year-old boy with past spirometry-confirmed diagnosis of asthma
- On salbutamol prn, with no controller medication
- Exercise or cold air-induced wheezing or cough 2x/week (uses salbutamol)
- Nighttime cough 1x/month
- FEV₁ is normal and at his best in clinic today
- 2 prior ED visits for asthma (+ dexamethasone), last was 2 years ago

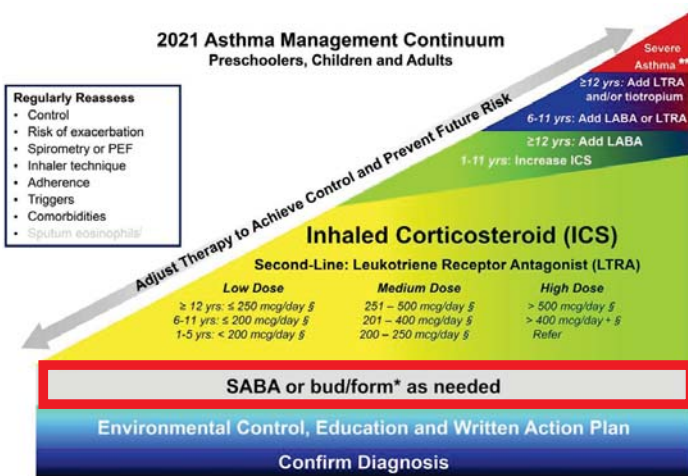
Case 1: Wayne

What would you recommend for this patient?

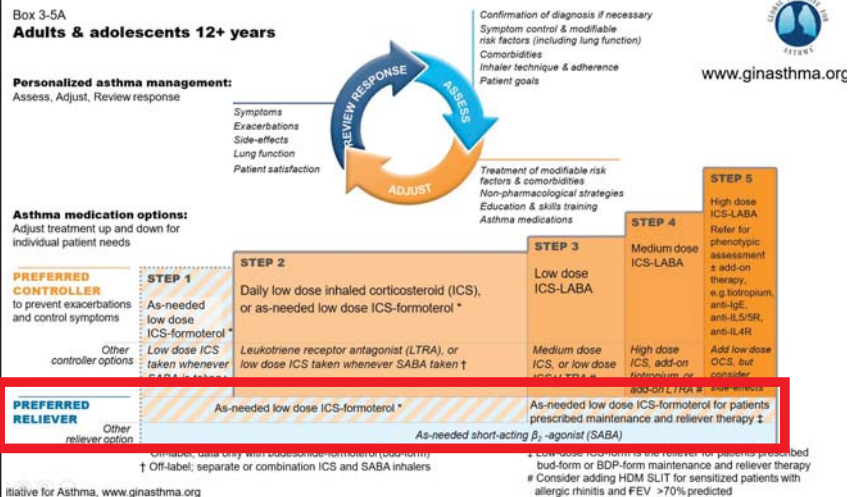
- A) PRN short-acting bronchodilator (SABA)
- B) PRN budesonide-formoterol
- C) PRN long-acting beta agonist (LABA)
- D) Daily low dose inhaled corticosteroid (ICS) and PRN SABA
- E) PRN SABA and PRN ICS every time that SABA is given

What's up with prn budesonide-formoterol?

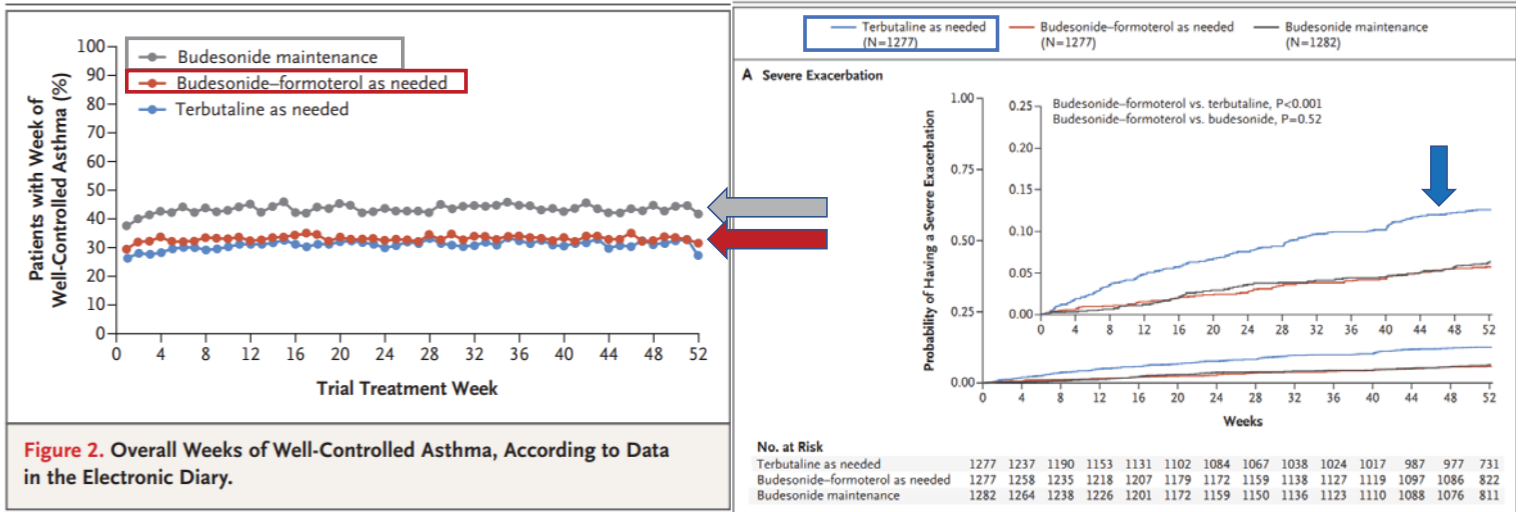
Canadian Thoracic Society (CTS)



Global Initiative for Asthma (GINA)

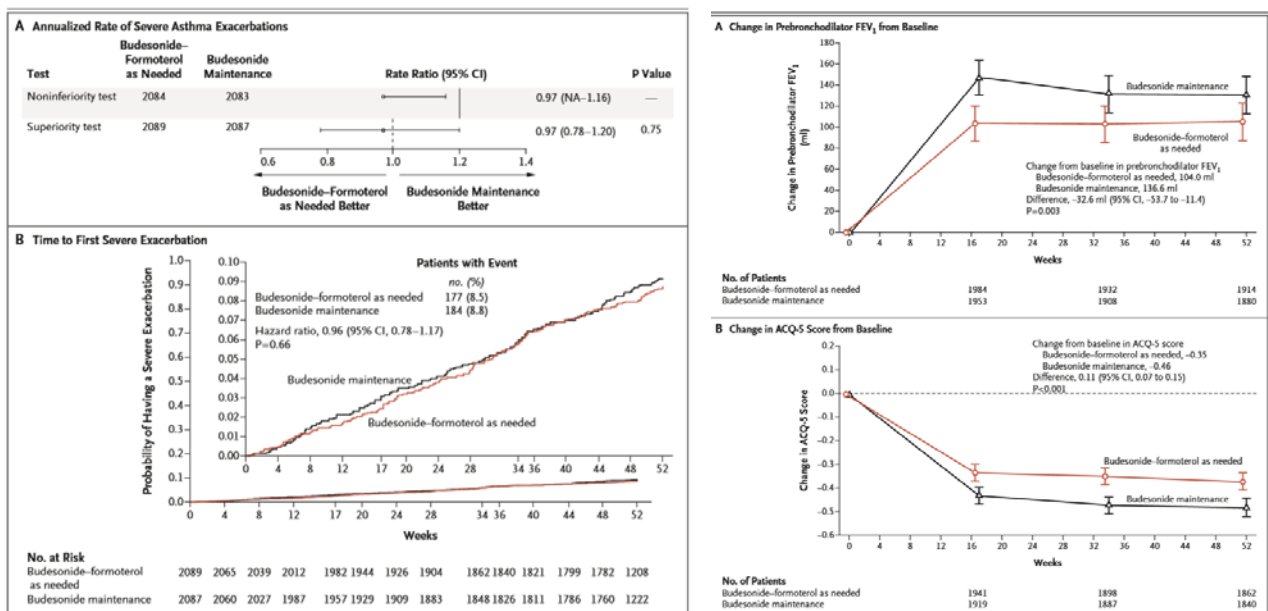


SYGMA1 (Symbicort Given as Needed in Mild Asthma) trial



N Engl J Med 2018;378:1865-76

SYGMA 2 (Symbicort Given as Needed in Mild Asthma) trial



N Engl J Med 2018;378:1877-87

Total ICS dose in SYGMA 1 and 2:

Median daily ICS dose in prn budesonide–formoterol grp was

17% (SYGMA 1)

25% (SYGMA 2)

of the dose in the budesonide maintenance group

https://www.reddit.com/r/aww/comments/2ru3m4/my_cat_has_asthma_this_is_the_look_i_get_every/

Our take-home from SYGMA 1 and 2

PROS of prn budesonide-formoterol (vs maintenance budesonide + prn terbutaline)

Non-inferior risk of severe exacerbation

Budesonide-formoterol was not overused in study

No increased risk of adverse events

Less total inhaled steroid dose

May be more appropriate for non adherent patients

CONS of prn budesonide-formoterol (vs maintenance budesonide + prn terbutaline)

Asthma control (symptoms) worse* - if relief of symptoms is goal and patient is adherent, maintenance budesonide likely better option)

Lung function not as good *

* But very small difference

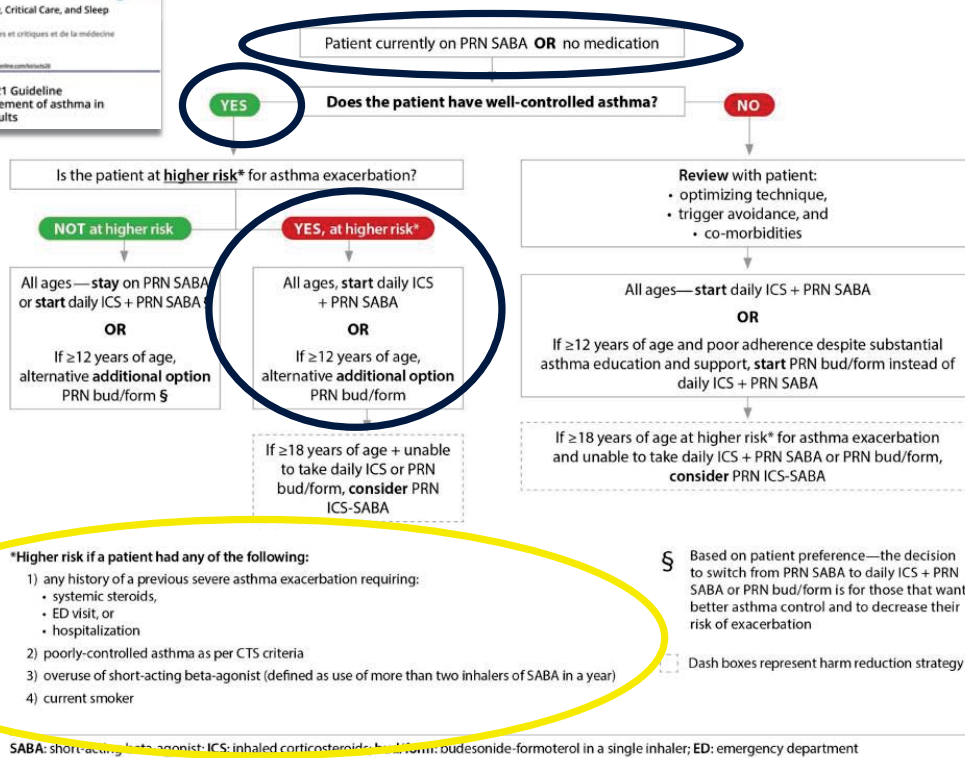


Figure 3. Treatment approach for patients on PRN SABA or no medication.

Wayne:
 14-y.o. on salbutamol prn
 No controller medication
 Symptoms 2x/wk
 Nighttime cough 1x/mo
 FEV₁ is at his best
2 prior ED visits for asthma (+ dexamethasone)

Case 1:
 Wayne mild, well controlled asthma, on no medications

What is the CTS-recommendation for this patient?

- A) PRN short-acting bronchodilator (SABA)
- B) PRN budesonide-formoterol (aka Symbicort)**
- C) PRN long-acting beta agonist (LABA)
- D) Daily low dose inhaled corticosteroid (ICS) and prn SABA**
- E) PRN SABA and prn ICS every time that SABA is given

Why is prn SABA incorrect in this patient?

Because he has had prior severe exacerbations

- Patients with mild asthma are still at risk for exacerbations
 - 30-40% of ER exacerbations are in patients with mild asthma
- SABA-only use is associated with
 - Higher risk of exacerbations
 - Lower lung function

Dusser et al, Allergy 2007: 62: 591–604
www.ginasthma.org (2019 Gina Guidelines)

Why is 'PRN ICS every time that PRN SABA is given' incorrect?

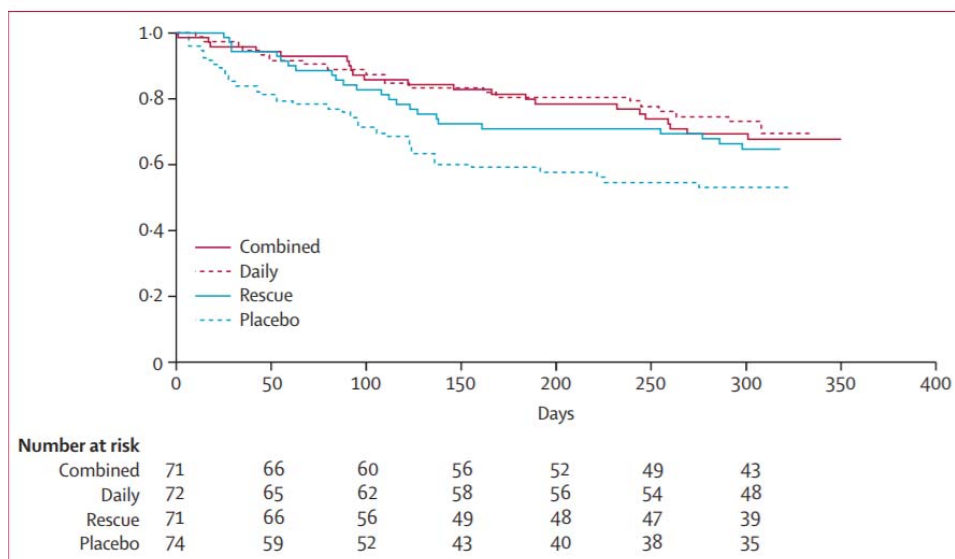
TREXA

	Maintenance	Prn 'rescue'
"Combined"	Bec	Alb + Bec
"Daily"	Bec	Alb + Placebo
"Rescue" (MCQ choice of discussion)	Placebo	Alb + Bec
"Placebo"	Placebo	Alb + Placebo

Bec = Beclomethasone
Alb=Albuterol

Lancet 2011; 377: 650–57

TREXA 1° outcome: time to first exacerbation requiring prednisone



	Hazard ratio* (95% CI)	Unadjusted p value	Hochberg adjusted p value
Daily beclomethasone main effect	0.66 (0.44-0.99)	0.033	..
Rescue beclomethasone main effect	0.84 (0.56-1.26)	0.280	..
Combined vs placebo	0.56 (0.32-0.96)	0.033	0.066
Daily beclomethasone vs placebo	0.49 (0.28-0.85)	0.011	0.033
Rescue beclomethasone vs placebo	0.62 (0.37-1.05)	0.073	0.073

*For pairwise comparisons, the hazard ratio is the group receiving beclomethasone compared with placebo. Hochberg adjusted p values are for comparison with the placebo group.

Table 2: Treatment effects

Figure 2: Kaplan-Meier curves showing the time to first exacerbation

Lancet 2011; 377: 650–57

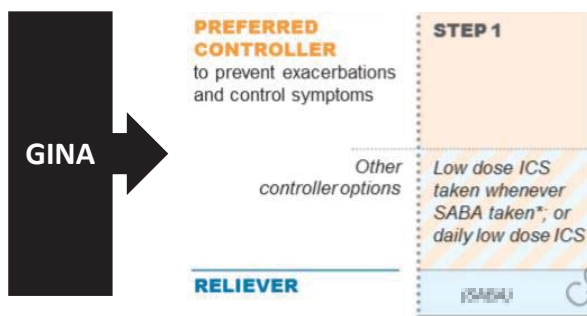
TREXA

	Maintenance	Prn 'rescue'	Exacerbation frequency compared to placebo + prn albuterol grp (49%)	Treatment failure (2x pred in 6 mo) compared to placebo + prn albuterol grp (23%)	Linear growth compared to placebo + prn albuterol grp
"Combined"	Bec	Alb + Bec	31%, p=0.07	5.6%, p=0.012	1.1 cm less, p<0.0001
"Daily"	Bec	Alb + Placebo	28%, p=0.03	2.8%, p=0.009	1.1 cm less, p<0.0001
"Rescue" (MCQ choice of discussion)	Placebo	Alb + Bec	35%, p=0.07	8.5%, p=0.024	No different
"Placebo"	Placebo	Alb + Placebo	49% (ref)	23% (ref)	ref

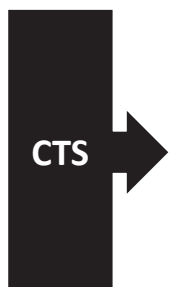
Bec = Beclomethasone
Alb=Albuterol

Lancet 2011; 377: 650-57

Why the controversy in ages 6-11...



GINA recommends these 2 options as equivalent but in TREXA, ICS maint+SABA prn was superior to ICS+SABA prn for time to exacerbations.



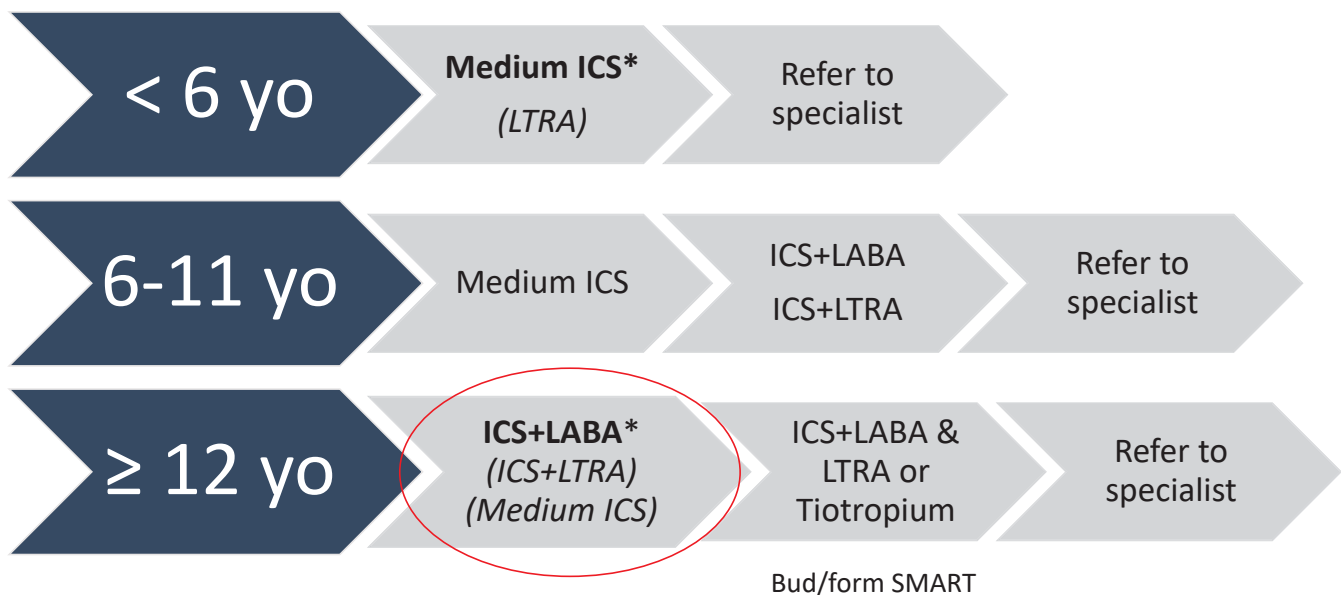
- **CTS** guidelines 2021 recommended *against* this approach in pediatrics
 - If recommending this off-label strategy, do not exceed the maximum approved daily ICS dose

Wayne is started on low-dose ICS and returns for follow-up 6 months later with poor control. **What is your next step?**

- If poor compliance:
 - discuss with patient
 - consider once daily ICS at equivalent dose
- Otherwise, once compliance, technique, other factors considered and ruled out:
 - Step up therapy



Step-up from low dose ICS



You start Wayne on Fluticasone-Salmeterol 125 mcg BID. He asks if he should take “extra puffs” when he is in the yellow zone?

Yellow zone

At any age:
Do not double ICS dose

≥16 yo with history of severe exacerbation:

- 4- 5 x ICS dose x 7-14 days
- Bud/form: max 4 inh BID x 7-14 d

(Yang et al, 2021)

Wayne is not adherent to BID Fluticasone-Salmeterol and asks if there is a once daily inhaler he could use instead?

Mometasone-indacaterol (Atectura)

- Ultra-long LABA, once daily
- ≥ 12 years old
- 3 dosing choices:
 - Low (80mcg)
 - Medium (160 mcg)
 - High (320mcg)

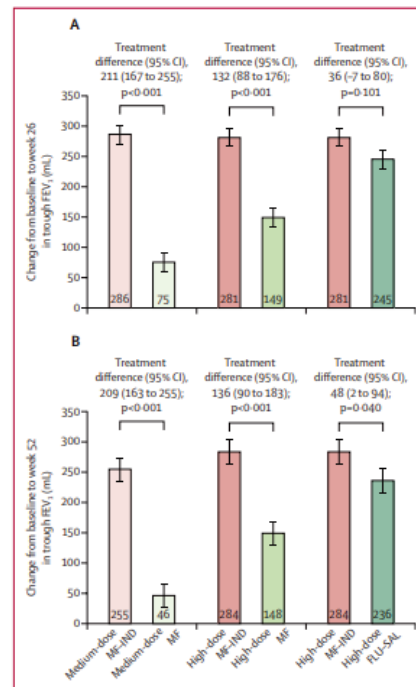


Figure 3: Change from baseline in trough FEV₁ at week 26 and week 52 in the full analysis set

(Van et al, 2020)

Take-home messages

- PRN SABA only for those with no risk factors
- PRN bud-form (Symbicort) is suggested for ≥ 12 yo with mild asthma with poor adherence to daily ICS
- PRN ICS with SABA is not supported by CTS
- No indication to double ICS dose in yellow zone but can quadruple if ≥ 16 yo
- For patients with poor control secondary to poor adherence, consider once daily options at equivalent doses



Thank you!
Questions?