

ASTHMA MANAGEMENT: (S)MART AND AIR

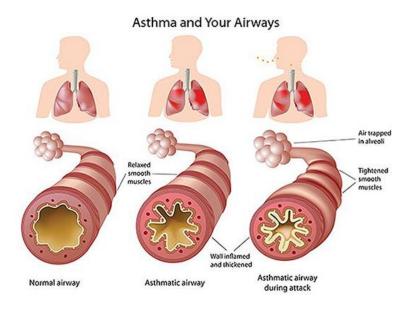
CHRISTINA KWONG MD PEDIATRIC ALLERGY/IMMUNOLOGY PHOENIX CHILDREN'S HOSPITAL JANUARY 30, 2025

DISCLOSURES

• Nothing to disclose.

ASTHMA

- Heterogenous disorder
- Contains multiple phenotypes and endotypes
- All phenotypes and endotypes → <u>reversible</u> airway obstruction from bronchial smooth muscle spasm and airway mucosal inflammation that causes variable expiratory airflow limitations



ASTHMA MORBIDITY

- Most common medical diagnosis among children hospitalized in the US; 260 million children affected worldwide
 - Accounts for >5% nonsurgical admissions to the hospital
- Leading cause for emergency care visits
- Leading cause for missed school
- This is despite asthma morbidity and mortality being largely preventable

ASTHMA MORBIDITY

- Oral steroid courses are not benign
- Adverse effects in the short and long term, including:
 - Growth impairment
 - Reduced bone mineral density
 - Behavioral effects
 - Increased infection susceptibility

Aljebab, F.Arch Dis Child 2016 Bleecker, E.WAO J 2022 Gray, N. JAMA Pediatr 2017 Kamada,AK. Pediatr Allergy Immunol 1995 Kelly, HM. Pediatr 2008 Papdopoulous, N. Pediatr Allergy Immunol 2018 Price, D. Eur Respir Rev 2020 Yao,TC. JAMA Pediatr 2021

ENTER...SMART THERAPY

DECREASING SABA USE AND INCREASING ICS/LABA



SMART: SINGLE MAINTENANCE AND RELIEVER THERAPY

- 2019 Global Initiative for Asthma (GINA) report first recommended as needed ICS-formoterol in 2019 for adolescents and adults
- The 2020 National Asthma Education and Prevention Program (NAEPP) guidelines preferentially recommended this for step 3 and 4 therapy in those 4 years and older
- Most recently updated in the GINA 2024 guidelines
- New terminology is **MART M**aintenance **A**nd **R**eliever **T**herapy with ICS-formoterol
- Another term is AIR Anti-Inflammatory Reliever

Why not treat with inhaled short-acting beta₂-agonists (SABA) alone?



- SABA treats the symptoms, but not the disease
- People with apparently mild asthma can have severe or fatal exacerbations (Dusser, 2007)
 - Up to 27% asthma deaths are in patients with occasional symptoms (Bergstrom, 2008)
 - Exacerbation triggers are unpredictable (viral, allergen, pollution, stress)
 - Even 4–5 lifetime OCS courses increase the cumulative risk of adverse events including osteoporosis, diabetes, cataract, heart failure, pneumonia (Price et al, J Asthma Allerg 2018)
- Regular use of SABA, even for 1–2 weeks, is associated with increased AHR, reduced bronchodilator effect, increased allergic response, increased eosinophils (e.g. Cockcroft 2006)
 - Can lead to a vicious cycle encouraging overuse
 - Over-use of SABA is associated with ↑ exacerbations and ↑ mortality (e.g. Suissa 1994, Nwaru 2020)
- Starting treatment with SABA trains the patient to regard it as their primary asthma treatment
 - Poor adherence with ICS is almost inevitable
- There is strong evidence for a more effective and safer alternative than SABA alone, or ICS plus as-needed SABA: as-needed ICS-formoterol

The blue one's good because you can just have a couple of squirts and get back to what you were doing

Cole et al, BMJ Open 2013

Why is GINA Track 1 with ICS-formoterol preferred?



- Steps 1–2: weight of evidence for effectiveness and safety compared with SABA alone, or low-dose ICS plus as-needed SABA (4x12 month studies, n~10,000) (Crossingham et al, Cochrane 2021)
 § As-needed ICS-SABA: only one 6-month RCT (n=455) (Papi et al, NEJMed 2007)
- Steps 3–5: weight of evidence for effectiveness and safety of MART versus regimens with as-needed SABA (n~30,000) (Sobieraj et al, JAMA 2018; Cates et al, Cochrane 2013)
 - § As-needed ICS-SABA: only one RCT (n=3,132) vs as-needed SABA (*Papi et al, NEJMed 2022*); cannot be used for maintenance and reliever therapy
- Both the ICS and the formoterol contribute to reduction in severe exacerbations (*Tattersfield et al, Lancet 2001; Pauwels et al, ERJ 2003; Rabe et al, Lancet 2006*)
 - § Safety established up to total 12 inhalations in any day, in large studies
- Simplicity of approach for patients and clinicians
 - § A single medication for both symptom relief and maintenance treatment (if needed) from diagnosis
 - § Avoids confusion about inhaler technique with different devices
 - § Short-term increase in symptoms à patient increases the number of **as-needed** doses
 - § Step treatment down or up by changing the number of maintenance doses

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O'Byrne et al, NEJM 2018

As-needed low-dose ICS-formoterol* in mild asthma (n=9,565)

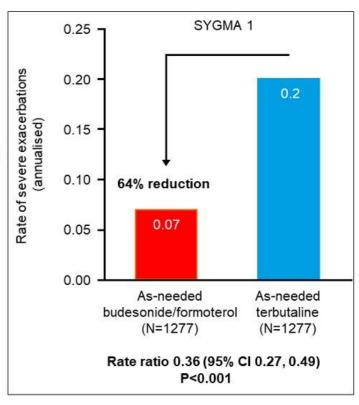
COMPARED WITH AS-NEEDED SABA

Risk of severe exacerbations reduced by 60–64% (SYGMA 1, Novel START)

COMPARED WITH MAINTENANCE LOW DOSE ICS plus as-needed SABA

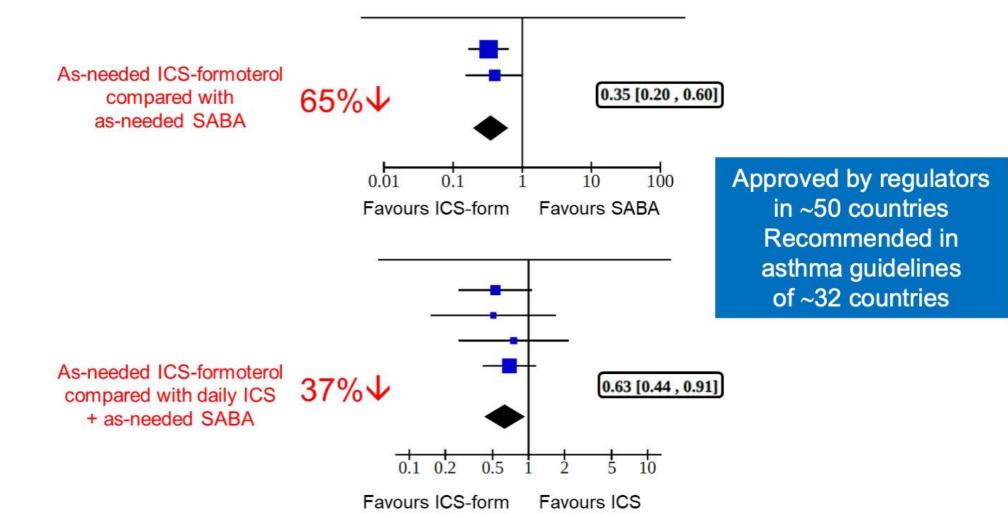
- Risk of severe exacerbations similar (SYGMA 1 & 2), or lower (Novel START, PRACTICAL)
- No clinically important differences in symptom control or FEV₁ (all 4 studies) or in FeNO (Novel START, PRACTICAL), and no worsening in these outcomes over 12 months
- Patients used the as-needed inhaler on ~30% of days: very low ICS dose
- Outcomes for severe exacerbations and ACQ-5 were independent of baseline characteristics including blood eosinophils, FeNO, lung function, history of exacerbations (Novel START, PRACTICAL)
- Embedded qualitative research demonstrated most patients preferred as-needed combination treatment over regular daily treatment (Baggott 2020 & 2022; Foster 2020 & 2022)

*Budesonide-formoterol 200/6 [160/4.5] mcg, 1 inhalation as needed for symptom relief

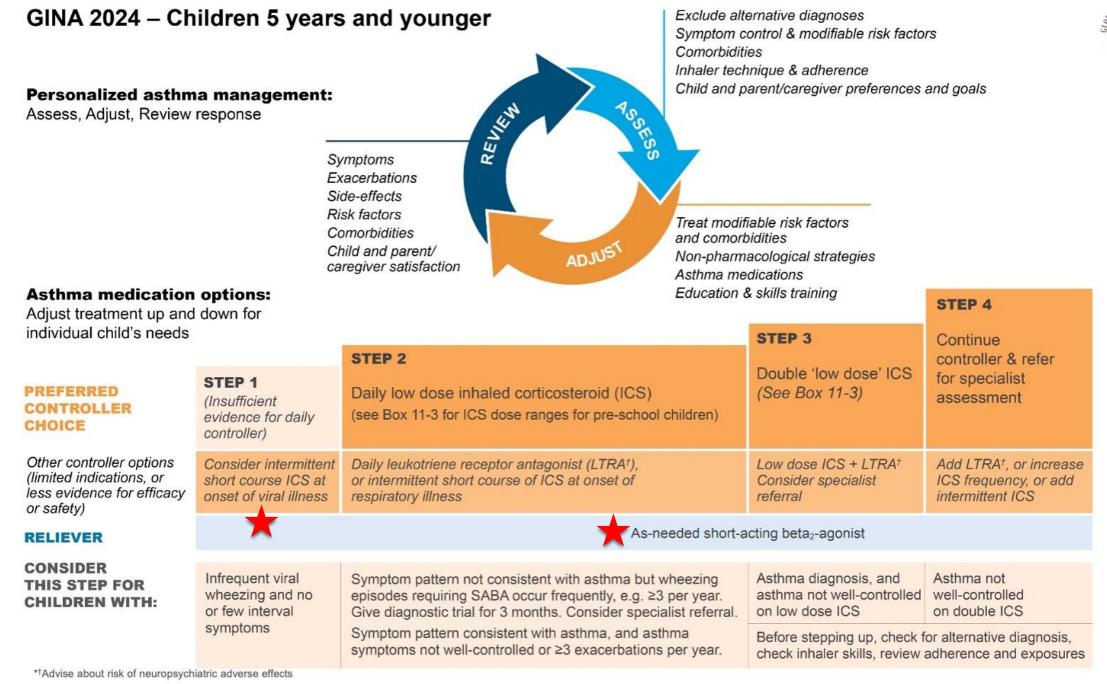




As-needed-only ICS-formoterol reduces emergency visits and hospitalisations in patients with mild asthma Odds ratio, 95% CI



From Crossingham et al, Cochrane Database Syst Rev 2021 (n=9565)



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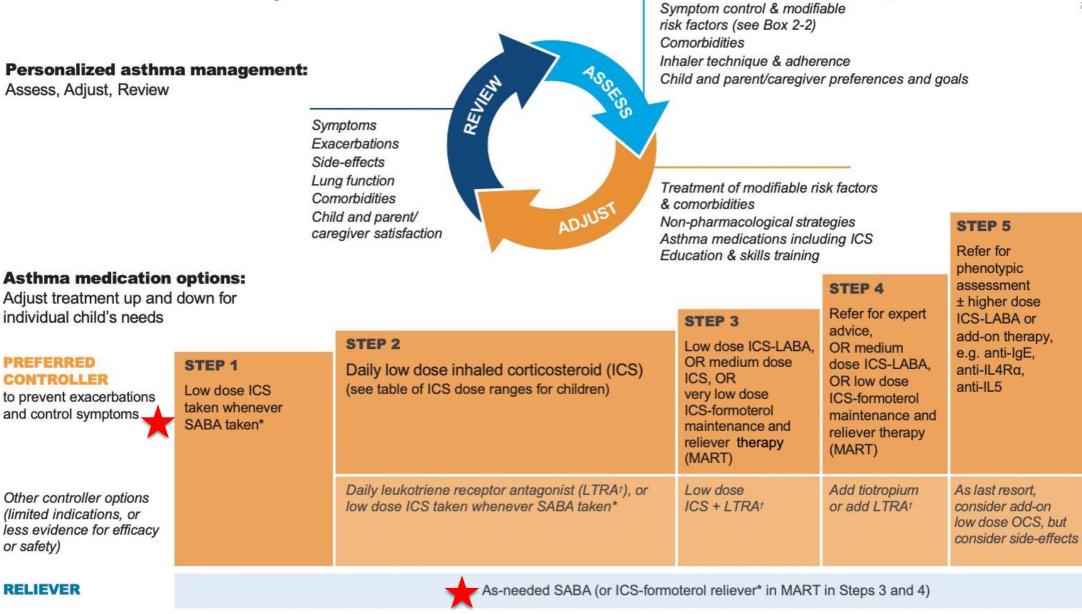
GINA 2024 – Children 6–11 years

Personalized asthma management:

Assess, Adjust, Review

PREFERRED

CONTROLLER



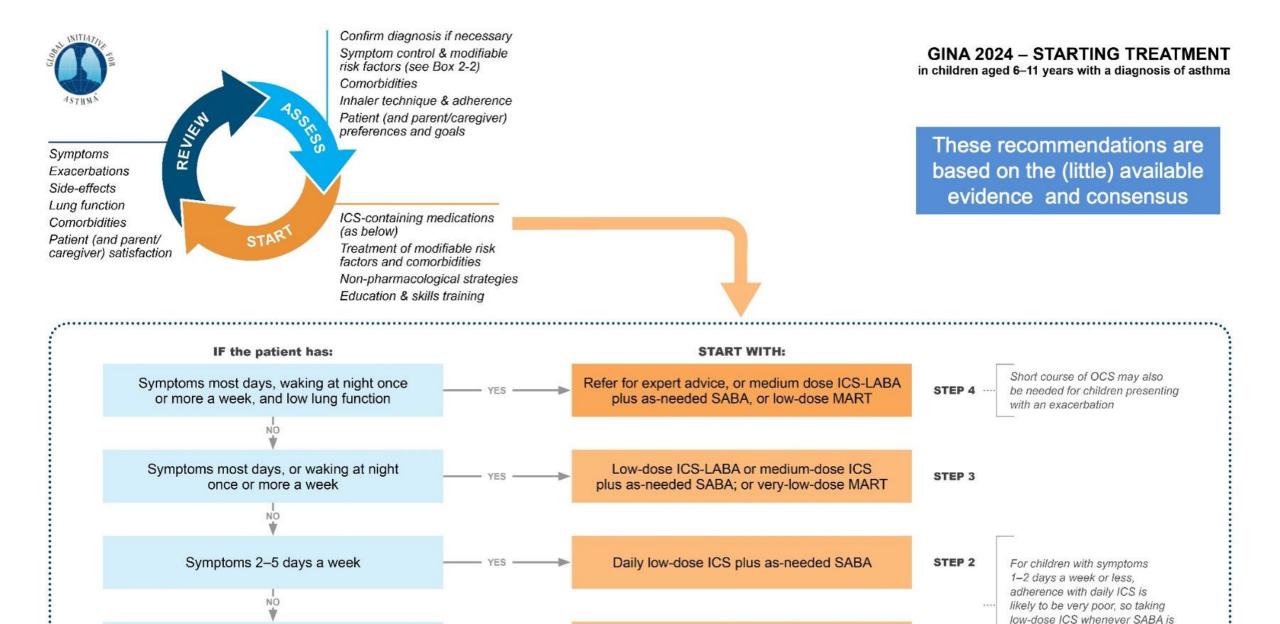
Confirmation of diagnosis if necessary

*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects

or safety)

RELIEVER





Take low dose ICS whenever SABA is taken

Symptoms less than two days a week

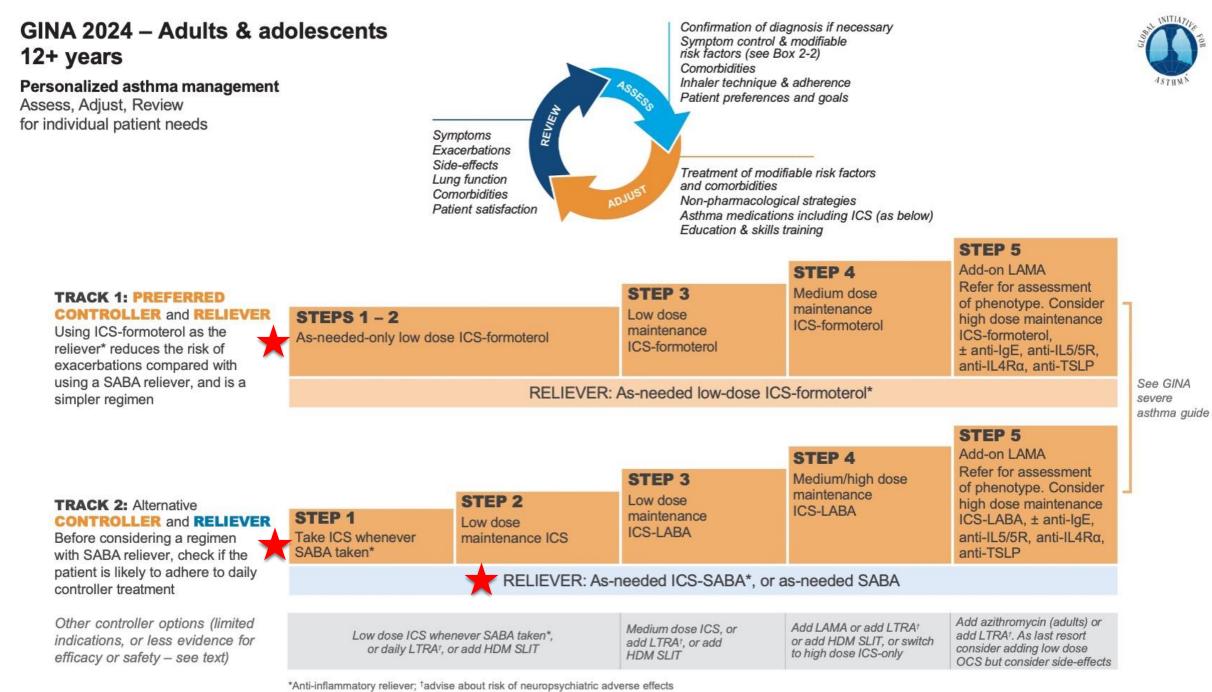
GINA 2024 Box 4-11

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taken may be a better option for

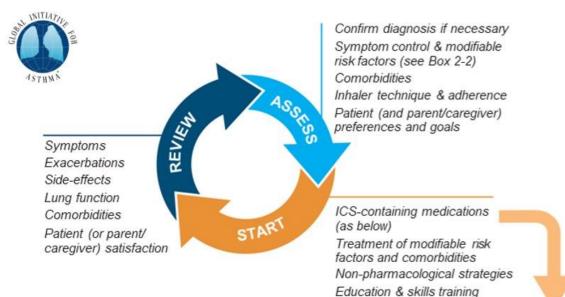
reducing exacerbation risk

STEP 1



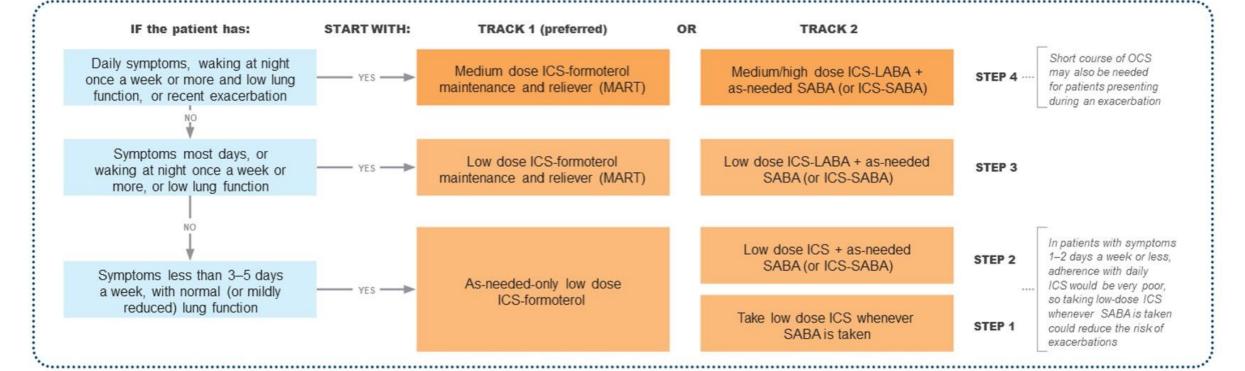
GINA 2024 Box 4-6

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GINA 2024 – STARTING TREATMENT in adults and adolescents 12+ years with a diagnosis of asthma

These recommendations are based on the (little) available evidence and consensus



GINA 2024 Box 4-5

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LET'S JUMP IN. HOW TO PRESCRIBE?

CHOOSING THE MEDICATION

- Studies primarily in budesonide-formoterol (Symbicort, Breyna)
 - Could consider mometasone-formoterol (Dulera)
- Recommended strengths and max inhalations are based on age
 - 6-11 years: 80/4.5, MAX 8 puffs per day
 - I2 years and older: I60/4.5 MAX I2 puffs per day
 - In studies, few patients have needed the max number
- Do not prescribe if another ICS-LABA is being used

DOSE RECOMMENDATIONS

MART Recommendations	Children 6-11 years 80/4.5 MAX 8 inhalations per day	Adolescents 12 and up 160/4.5 MAX 12 inhalations per day
Step I	N/A	l inhalation as needed
Step 2	N/A	l inhalation as needed
Step 3	I inhalation once daily + I as needed	I inhalation once or twice a day plus I as needed
Step 4	I inhalation once daily + I as needed	2 inhalations twice daily + I as needed
Step 5	Not recommended	2 inhalations twice daily + I as needed

TAKE HOME MESSAGE

NO SABA only. Also need ICS.

For asthmatics 6 years and older

POTENTIAL PROVIDER QUESTIONS

- Does ICS-LABA work as quickly as a SABA for symptom and bronchoconstriction relief
 - Yes, same onset of action but the LABA lasts longer
- Is it safe?
 - Yes
 - Supported by a lot of evidence (Pool analysis of 6 DBRCT and 7 open label clinical trials, Cochrane Review of 13 trials, 2020 NAEPP Asthma Update recommendation)
- Will patients be less adherent to their maintenance dosing since the same medication is available for rescue?
 - It's possible, but studies have shown overall increased ICS-LABA use
- How much to prescribe for MART: Two budesonide-formoterol inhalers per month, but this is not always covered

THE ASTHMA PLAN

Asthma and Allergy Foundation of America aafa.org

The colors of a traffic light will help you use your asthma medicines.

GREEN means Go Zone! Use preventive medicine.

YELLOW means Caution Zone! Add quick-relief medicine.

RED means Danger Zone! Get help from a doctor.

Personal Best Peak Flow:

Name:

Doctor:

Doctor's Phone #: Day

Emergency Contact:

Doctor's Signature:

ASTHMA ACTION PLAN

Date:

Medical Record #:

Night/Weekend

GO		Use these daily controller medicines:		
You have all of these: • Breathing is good • No cough or wheeze • Sleep through the night • Can work & play	Peak flow: from to	MEDICINE	HOW MUCH	HOW OFTEN/WHEN
CAUTION		Continue with green zone medicine and add:		
You have <i>any</i> of these: • First signs of a cold • Exposure to known trigger • Cough • Mild wheeze • Tight chest • Coughing at night	Peak flow: from to	MEDICINE	HOW MUCH	HOW OFTEN/ WHEN
DANGER		Take these medicines a	nd call your docto	or now.
Your asthma is getting • Medicine is not helping • Breathing is hard & fast • Nose opens wide • Trouble speaking • Ribs show (in children)	Peak flow: reading below	MEDICINE	HOW MUCH	HOW OFTEN/WHEN

GET HELP FROM A DOCTOR NOW! Your doctor will want to see you right away. It's important! If you cannot contact your doctor, go directly to the emergency room. DO NOT WAIT. Make an appointment with your asthma care provider within two days of an ER visit or hospitalization.

THE ONE-SIZE-FITS ALL PLAN

- Included in the PCCN Asthma Network Guide
- Can use for all asthma patients
- Will need to add MART/AIR specific info

https://aafa.org/wp-content/uploads/2022/10/asthma-action-plan-aafa.pdf

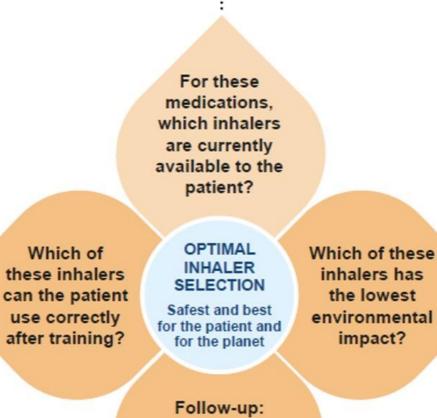
 and (0, 1, 2) initial attories in the evening, every day Reliever Use 1 inhalation of budesonide/formoterol whenever needed for relief of my asthma symptoms I should always carry my budesonide/formoterol inhaler My asthma is stable if: I can take part in normal physical activity without asthma symptoms ND I do not wake up at night or in the morning because of asthma If I need more than 12 budesonide/formoterol inhaltions (total) in any day, (or more than Start a course of prednisolone tablets (as directed)	My Asthma Action Plan For Single Inhaler Maintenance and Reliever Therapy (SMART) with budesonide/formoterol	Name:	Doctor:
 Any contrart return r	Normal mode	Asthma Flare-up	Asthma Emergency
Other Instructions 8 inhalations for children 4-11 years) while waiting for the ambulance I MUST see my doctor or go to the hospital • Even if my symptoms appear to settle quickly, I should see my doctor immediately after a serious attack	 budesonide/formoterol 160/4.5 (12 years or over) budesonide/formoterol 80/4.5 (4-11 years) M Pegular Treatment Every Day: Write in or circle the number of doses prescribed for this patient) Take [1, 2] inhalation(s) in the morning and [0, 1, 2] inhalation(s) in the evening, every day Reliever Use 1 inhalation of budesonide/formoterol symptoms Is hould always carry my budesonide/formoterol inhaler My asthma is stable if: 1 can take part in normal physical activity without asthma symptoms Hou And <li< td=""><td> My asthma symptoms are getting worse OR NOT improving OR I am using more than 6 budesonide/formoterol reliever inhalations a day (if aged 12 years and older) or more than 4 inhalations a day (if 4–11 years) I should: Continue to use my regular everyday treatment PLUS 1 inhalation budesonide/formoterol whenever needed to relieve symptoms Start a course of prednisolone Contact my doctor Course of Prednisolone Tablets: Take mg prednisolone tablets per day for a use days OR If I need more than 12 budesonide/formoterol inhalations (total) in any day, (or more than 8 inhalations for children 4-11 years) IMUST see my doctor or go to the hospital </td><td> Symptoms getting worse quickly Extreme difficulty breathing or speaking Little or no improvement from my budesonide/formoterol reliever inhalations. If I have any of the above danger signs, I should dial and for an ambulance and say I am having a severe asthma attack. While I am waiting for the ambulance start my asthma first aid plan: Sit upright and stay calm Take 1 inhalation of budesonide/formoterol. Wait 1-3 minutes. If there is no improvement take another inhalation of budesonide/formoterol (up to a maximum of 6 inhalations on a single occasion) If only albuterol is available, take 4 puffs as often as needed until help arrives Start a course of prednisolone tablets (as directed) while waiting for the ambulance Even if my symptoms appear to settle quickly, I should see my doctor immediately after </td></li<>	 My asthma symptoms are getting worse OR NOT improving OR I am using more than 6 budesonide/formoterol reliever inhalations a day (if aged 12 years and older) or more than 4 inhalations a day (if 4–11 years) I should: Continue to use my regular everyday treatment PLUS 1 inhalation budesonide/formoterol whenever needed to relieve symptoms Start a course of prednisolone Contact my doctor Course of Prednisolone Tablets: Take mg prednisolone tablets per day for a use days OR If I need more than 12 budesonide/formoterol inhalations (total) in any day, (or more than 8 inhalations for children 4-11 years) IMUST see my doctor or go to the hospital 	 Symptoms getting worse quickly Extreme difficulty breathing or speaking Little or no improvement from my budesonide/formoterol reliever inhalations. If I have any of the above danger signs, I should dial and for an ambulance and say I am having a severe asthma attack. While I am waiting for the ambulance start my asthma first aid plan: Sit upright and stay calm Take 1 inhalation of budesonide/formoterol. Wait 1-3 minutes. If there is no improvement take another inhalation of budesonide/formoterol (up to a maximum of 6 inhalations on a single occasion) If only albuterol is available, take 4 puffs as often as needed until help arrives Start a course of prednisolone tablets (as directed) while waiting for the ambulance Even if my symptoms appear to settle quickly, I should see my doctor immediately after

A FEW NOTES FOR PATIENTS

- Can the ICS/LABA be used for exercise pretreatment?
 - Yes, if available. It provides greater protection from exercise-induced bronchconstriction
- What should be used at school?
 - If ICS-formoterol is not available, use SABA instead
- What if they reach the max number of puffs?
 - Use albuterol or seek emergency treatment per plan. But in studies, reaching the max number was uncommon.
- What about in the Red Zone?
 - Use Albuterol if max doses of ICS-formoterol used
- Rinse mouth after ICS/LABA
- Let the provider know if there are issues getting the inhaler(s) or if it is cost prohibitive.

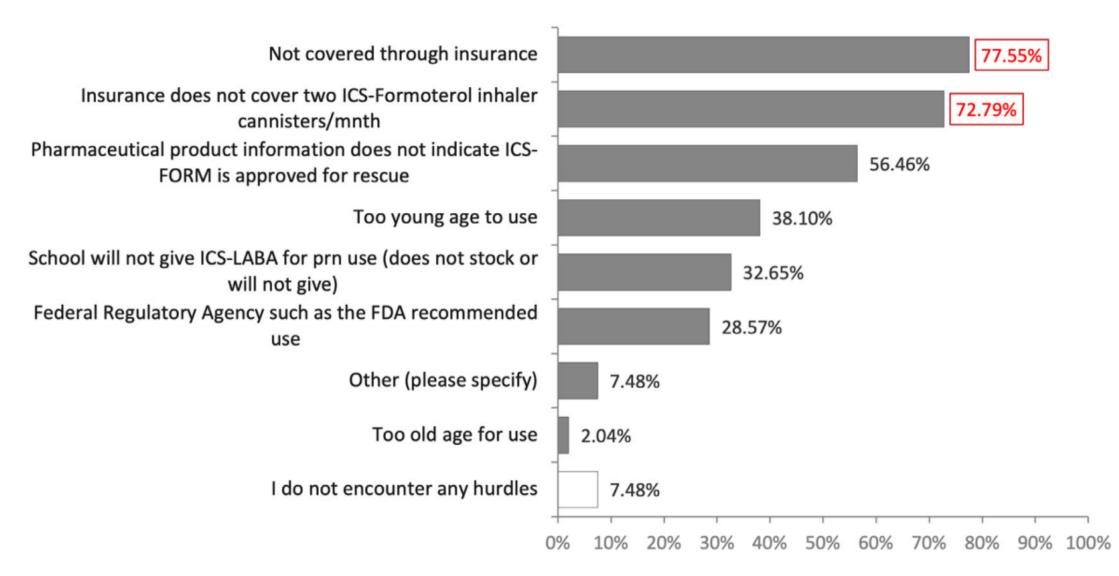
For this patient, which is the right class of medication?





Is the patient satisfied with the medication(s) and inhaler(s)?

Hurdles for prescribing one's preferred ICS-formoterol use



Bacharier, LB. 2023 ACAAI Annual Meeting Plenary Lecture

WHAT'S THE PROBLEM?

- (S)MART therapy is approved in over 120 countries
- BUT, most trials used the dry powder inhaler form and NOT the pressurized metered-dose inhaler (pMDI)
- To change the indication, supporting clinical trial data with the pMDI are needed
- So, ICS-formoterol inhalers are not FDA approved as rescue inhalers or for (S)MART therapy in the United States
 - Disclaimers are required
- Insurance coverage challenges also exist
 - Cost differences between SABA and ICS-LABA
 - Dispensing quantity limits
 - AHCCCS: step-up requirement removed thanks to PCCN, dispenses one inhaler only
 - Cigna: may require prior auth, allows for two inhalers

WHAT TO DO?

- We encourage continued prescribing of MART and AIR therapies since these treatments are proven to be effective
 - It is possible to use MART therapy in many eligible patients. Shared decision making and follow up is helpful
 - Understanding up-to-date payor practices is important
- Feel free to reach out to our Phoenix Children's specialists!
 - Our Allergy Immunology and Pulmonary divisions have physicians that specialize in treating the full range of asthma severities.
- We want to be a resource and support you, whether it's seeing a patient once to offer input, following long term or anything else
- Also, the Severe Asthma Clinic is a multidisciplinary clinic with both specialties and pharmacy support

ALSO AVAILABLE: CURRENT RESEARCH AND CAMP

- EAGLE: OM-85 (bacterial lysate) in 6 months to 5 year olds with wheezing episodes in the past year
- HORIZON: Tezepelumab in 5 to 11 year olds with severe asthma
- TREKIDS: Dupilumab in 2 to <6 year olds with uncontrolled asthma
- Upcoming ARIA: Trelegy Ellipa vs Breo Ellipta in 12-17 year ols with asthma
- Fun and educational asthma camp: Camp Not a Wheeze, June 1-7, 2025.
 - Camp Shadow Pines, Heber, AZ
 - <u>https://campnotawheeze.org</u>
 - If interested in flyers, can email info@campnotawheeze.org or Dr. Cindy Bauer at cbauer@phoenixchildrens.com.

ASTHMA MANAGEMENT FOCUS

- Phoenix Children's Care Network is continuing to make asthma management and provider support a high priority this year.
- Focus areas include:
 - (S)MART therapy
 - Asthma Action Plans
 - Asthma Control Test Scores
 - Asthma Medication Ratio information
- PCCN is continuing to evolve its resources to best help providers navigate these challenging but also very
 promising asthma management advances.



NOT DONE YET – LAST SECTION!

REVIEWING ASTHMA INHALERS: NAVIGATING THE MAZE OF WHAT'S COVERED BY INSURANCE AND APPROPRIATE FOR THE PATIENT CAN BEVERY TOUGH

RECENT ASTHMA INHALER CHANGES

- GSK discontinued branded Flovent on Jan 1, 2024. Generics for Flovent HFA and Flovent Diskus are available.
- Teva is discontinuing all Digihaler products (ProAir, AirDuo, ArmonAir). ProAir and AirDuo Respiclick will still be available.
- \$35 per month out of pocket caps on some inhalers

Boehringer Ingelheim	AstraZeneca	GSK
Caps started June I st 2024	Caps started June I st 2024	Caps started no later than Jan I 2025
Atrovent HFA (ipratropium)	Symbicort (budesonide and formoterol fumarate, Breyna not listed)	Advair Diskus/HFA (fluticasone propionate and salmeterol)
Combivent Respimat (ipratropium/albuterol)		Arnuity Ellipta (fluticasone furoate)
Spiriva Handihaler/Respimat		Breo Ellipta (fluticasone and vilanterol)
		Ventolin HFA





For questions or assistance please call us at 1-800-236-9933 (Monday–Friday, 8 AM–6 PM ET, excluding holidays)

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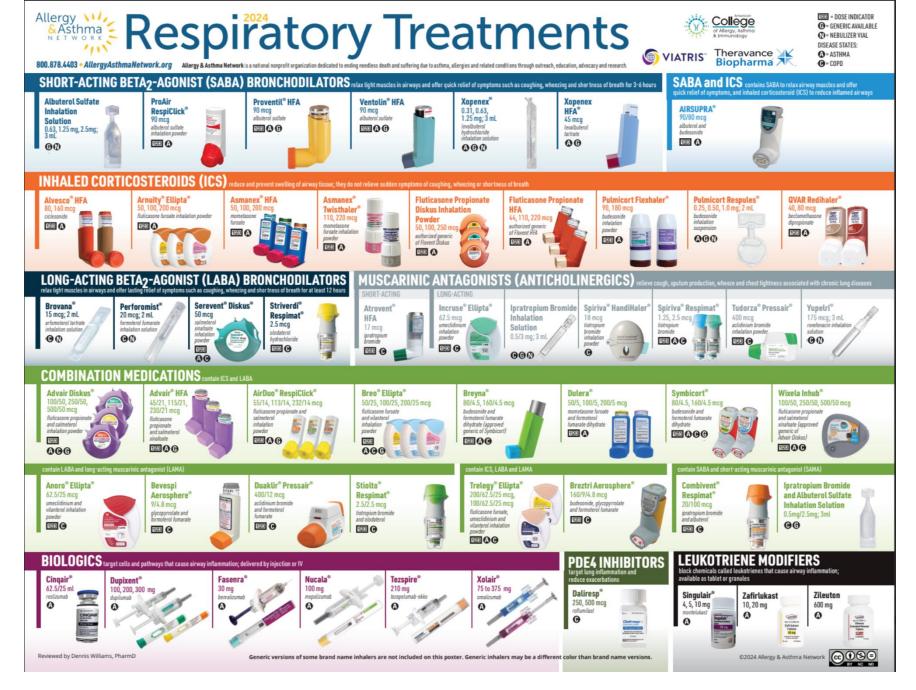
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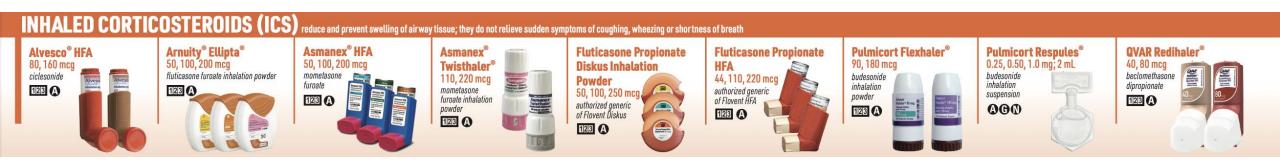
MEDICARE

for Patients and

Providers



https://store.allergyasthmanetwork.org/digital-downloads/respiratory-treatments-digital-english-version-11-x-8-1-2



- Flovent Alternatives:
 - 4 and under: Pulmicort resputes (approved 12 months-8 years), Fluticasone HFA (approved for 4 and older), Asmanex Twisthaler and Fluticasone Diskus are also approved at age 4 but proper technique may be an issue
 - 5 and over: Can also use Asmanex HFA, Arnuity Ellipta (need to confirm breath-activated technique ability)
 - 6 and older: Can also use Pulmicort Flexhaler, Qvar Redihaler (need to confirm breath-activated technique)
 - Although Qvar is approved for 4 and older, there are likely technique concerns when <6
 - **I 2 and older:** Can also use Alvesco HFA
- Breath-activated inhalers are NOT used with a spacer

COMBINATION MEDICATIONS contain ICS and LABA



- Name-brands
 - Advair Diskus: 4 years and older (but 4-5 year olds may have technique limitations)
 - Advair HFA: 12 years and older
 - Breo Ellipta: 5 years and older (expanded approval in 2023, previously 18+)
 - Dulera HFA: 5 years and older
 - Symbicort HFA: 6 years and older
 - AirDuo : 12 years and older
 - Same medication as Advair HFA, lower dose of salmeterol, uses a respiclick device
- Generic
 - Wixela Inhub (fluticasone/salmeterol) for Advair: 4 years and older (but 4-5+ year olds may have technique limitations)
 - Breyna (budesonide/formoterol) for Symbicort: 6 years and older, approved in 2023



THANK YOU!

ANY QUESTIONS OR COMMENTS?

Feel free to reach out!

ckwong@phoenixchildrens.com