Asthma Guideline Updates: 2020 NHLBI Focused Update and 2020 GINA

Executive Summary: It is recommended to use low dose scheduled ICS-formoterol plus PRN ICS-formoterol before moving up to a medium dose ICS for mild and moderate persistent asthma. GINA 2020 recommends ICS-formoterol as the preferred reliever therapy at any Step of therapy, while NHLBI indicates that PRN SABA remains appropriate for intermittent asthma and can be used in combination with other types of inhalers or as an alternative for mild and moderate persistent asthma. Recommend weighing the risks of PRN SABA against the potential benefits of ICS-formoterol, and consider formulary coverage/days' supply limits.

The 2020 Focused Updates to the Asthma Management Guidelines from NHLBI[1] updated their recommendations for management of mild to moderate persistent asthma, recommending preferred treatment with daily and PRN low dose ICS-formoterol in Step 3, also defined as SMART (single maintenance and reliever therapy). GINA 2020 recommends ICS-formoterol as the preferred reliever inhaler at all steps of treatment.

Evidence Summary

Support for the use of SMART (single maintenance and reliever therapy) vs. Higher-Dose ICS in step 3 of the NHLBI guidelines is based off of 3 randomized controlled trials[3-5]. The intervention included patients treated with daily budesonide-formoterol, 160/9 to 320/9 mcg, and used up to 10 rescue puffs of budesonide-formoterol. The control group used daily budesonide, 320-640 mcg, along with SABA for rescue therapy. The 3 studies showed a 51%[3], 35%[4], and 43%[5] RR reduction in exacerbations. Total asthma symptom scores, nighttime awakenings, symptom-free days, and asthma control days significantly favored SMART and the overall doses of inhaled and oral corticosteroids were significantly lower with SMART.

Support for the use of SMART vs. Same-dose ICS-LABA controller therapy + SABA rescue is based off of 4 blinded[3,6-8], and 2 unblinded[9-10] randomized controlled trials. Collectively they found a 32% reduction in exacerbations with SMART. Two of these studies used validated asthma control measures and found clinically significant improvements with SMART.[8,10]

The use of ICS-formoterol in treatment steps 1 and 2 of the NHLBI guidelines was not included in the six priority topics that were identified for the 2020 update, therefore recommendations have not changed from SABA as the preferred reliever in steps 1 and 2.

GINA based recommendations for ICS-formoterol as the preferred reliever at any step of therapy from indirect evidence from a large double-blind study comparing it to SABA-only treatment and low dose ICS plus PRN SABA and two open-label randomized controlled trials. PRN ICS-formoterol was associated with a 60% reduction in severe exacerbations compared to PRN SABA. Increased asthma related death, even with good symptom control can be seen in those on PRN SABA monotherapy.

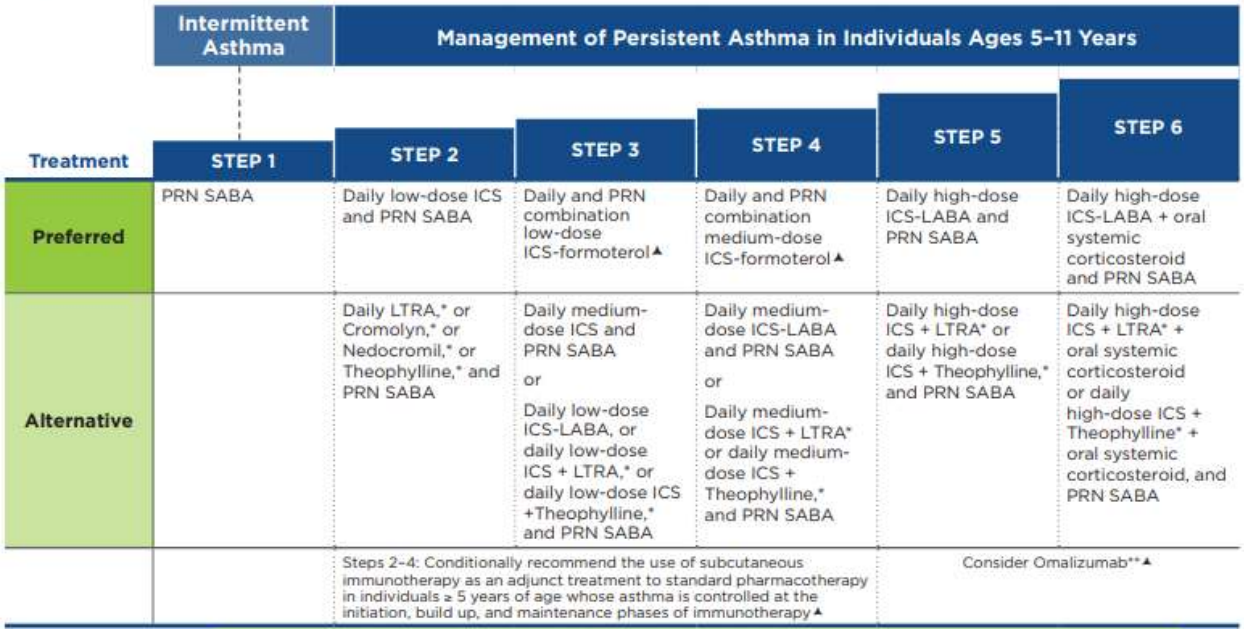
Tips for prescribing SMART (single maintenance and reliever therapy)
Sig: 2 inhalations BID plus 1-2 puffs prn symptoms
Add maximum dose: 12 inhalations per day maximum
Don't use combinations with salmeterol or vilanterol as bronchodilation can take 15 to 30 minutes or more with these LABAs

Avera Health Insurance Division considerations:
Budesonide-formoterol (Tier 1 – generic) – Quantity Limit = 2 inhalers per 30 days

Figure I.d: Stepwise Approach for Management of Asthma in Individuals Ages 12 Years and Older

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6 ■
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* 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 adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

Figure I.c: Stepwise Approach for Management of Asthma in Individuals Ages 5–11 Years



	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**▲	

2020 NHLBI Focused Updates, Figures I.d and I.c

Take-Aways

- SABA use >2 days weekly for symptom relief indicates sub-optimal control, may require a step up in therapy
- Max daily dose of ICS-formoterol is **8 puffs** for ages 5-11 and **12 puffs** for ages 12+
- Formoterol is the only studied LABA for PRN use along with ICS. Formoterol has faster onset of action, supporting its rationale for acute symptoms.
- Formulary coverage and days' supply of ICS/formoterol may be variable

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Overview of Agents for Asthma Treatment

Executive Summary: Initial pharmacotherapy should be based on patient's symptom frequency (see step tables in 2021 GINA guidelines and 2020 NHLBI guidelines; note different tables for ages 6-11 and ages 12 and up). Growing options of controller inhalers (including some generics) provide more options for prescribers to tailor therapy to each patient's needs; see comparison chart below.

Highlights of Most Common Inhaler and Nebulizer Options

See 2020 asthma guidelines, Avera Inhaled Corticosteroid Dosing Chart or each medication's package insert for dosing appropriate for each step of therapy. Not all doses or inhalers are indicated for all age groups.

Common Inhaler Comparison

Sorted by approximate cost, low to high, within each pharmacologic class

*Avera Health Plans preferred products within each pharmacologic class at time of publication are noted with an asterisk

Brand name only options highlighted in red	Generic alternatives to brand name options highlighted in yellow	Generic options highlighted in green

Generic name	Brand Name & Status	Cost ($ to $$$)	Advantages	Disadvantages
ICS Monotherapy				
Budesonide nebulizer suspension	Pulmicort Respules* Generic available	$	May provide greater dose delivery for patients with poor respiratory drive. Indicated age 12 months to 8 years.	Inconvenient for dosing on-the-go.
Fluticasone DPI	Arnuity Ellipta* Brand only; has generic alternatives which may or may not be less expensive	$	Once daily dosing. Easy to use for patients of all indicated ages.	DPI difficult for patients with poor respiratory drive. Only indicated ages 12 and older.
Beclomethasone HFA	QVAR Redihaler* Brand only	$$	Easy to use for all indicated ages - no shaking, pressing, or spacer needed. Indicated age 4 and older.	Twice daily dosing.

Budesonide Dry Powder Inhaler (DPI)	Pulmicort Flexhaler* Brand only	$$	Indicated age 6 and older.	Twice daily dosing, DPI difficult for patients with poor respiratory drive.
Fluticasone HFA	Flovent HFA* Brand only	$$	HFA may provide deeper dose delivery for patients with poor respiratory drive. Indicated ages 4 years and older.	Twice daily dosing.
Fluticasone DPI	Flovent Diskus* Brand only; has generic alternatives which may or may not be less expensive	$$	Easy to use for patients of all indicated ages. Indicated ages 4 years and older.	DPI difficult for patients with poor respiratory drive, twice daily dosing.
Mometasone DPI	Asmanex Twisthaler* Brand only	$$	Starting doses may be once daily. Easy to use for patients of all indicated ages. Indicated ages 4 years and older.	DPI difficult for patients with poor respiratory drive.
Mometasone HFA	Asmanex HFA Brand only	$$	HFA may provide deeper dose delivery for patients with poor respiratory drive. Indicated ages 5 years and older.	Twice daily dosing.
Fluticasone DPI	ArmonAir Digihaler Generic alternative; may not be AB-rated to other fluticasone inhalers	$$$	Contains built-in sensors to connect to a mobile app which provides information on proper use.	DPI difficult for patients with poor respiratory drive. Only indicated ages 12 and older.
ICS-LABA Combination Agents				
Budesonide / formoterol HFA	Symbicort* Generic available	$$	Can use for reliever due to formoterol quick onset. HFA may provide deeper dose delivery for patients with poor respiratory drive. Indicated ages 6 years and older.	Cost can add up if used as controller plus reliever.
Fluticasone / salmeterol DPI	Advair Diskus*	$$	Easy to use for patients of all	Twice daily dosing.

	Generic available; has generic alternatives which may or may not be less expensive		indicated ages. Indicated ages 4 years and older.	
Fluticasone / salmeterol DPI	AirDuo Respiclick Generic alternative	$$$	Generic alternative to Advair (although not AB-rated equivalent, dosing different)	Only indicated ages 12 and older, DPI difficult for patients with poor respiratory drive.
Fluticasone / salmeterol HFA	Advair HFA Brand only	$$$	HFA may provide deeper dose delivery for patients with poor respiratory drive	Twice daily dosing. Only indicated ages 12 and older.
Fluticasone / salmeterol DPI	Advair Diskus* Generic available; has generic alternatives which may or may not be less expensive	$$$	Easy to use for patients of all indicated ages. Indicated ages 4 years and older.	Twice daily dosing
Mometasone / formoterol HFA	Dulera Brand only	$$$	Can use for reliever due to formoterol quick onset. HFA may provide deeper dose delivery for patients with poor respiratory drive. Indicated for ages 5 years and older.	Cost can add up if used as controller plus reliever.
LAMA Agent				
Tioptropium	Spiriva Respimat* Brand only	$$$	Provides better quality dose than Spiriva Handihaler (generally not preferred any longer) and other dry powder inhalers. Indicated for ages 6 years and older for asthma.	Can be challenging for patient to learn how to assemble and prime device.
ICS – LABA – LAMA Combination Agent				
Fluticasone / vilanterol / umeclidinium DPI	Trelegy Ellipta* Brand only	$$$+	Once daily dosing, easy for patients of all indicated ages to use.	Only indicated for patients age 18 and older for asthma.

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Asthma – Checklist Prior to Initiating Biologics

Executive Summary: When treating more severe asthma, a number of considerations should be taken to optimize therapy prior to initiating biologics as detailed in the guide Avera When to Consider a Biologic Agent for Severe Asthma. Growing evidence on efficacy and risks of various treatment point prescribers toward new prescribing techniques, but in some cases inhaler technique, spacer device, or improved adherence may improve outcomes without making a medication change.

Step 5 Asthma Treatment Inhaler Options

- High-dose Inhaled Corticosteroid (ICS) – Long-Acting Beta Agonist (LABA) combination may be considered, but the increase in ICS may not provide much benefit at the cost of increased side effects, including adrenal suppression. If this high-dose option is utilized, it should only be done on a trial basis for three to six months.
- Adding on a long-acting muscarinic antagonist (LAMA) such as tiotropium on to ICS-LABA therapy in patients with asthma age 6 and older is an option if asthma is not controlled with a medium dose ICS-LABA. Utilizing a triple therapy inhaler such as fluticasone furoate-vilatnterol-umeclidinium (Trelegy) is another option that some patients will find more simple.
- The addition of a LAMA may improve lung function and extend time to severe exacerbation requiring oral corticosteroids, but it has not demonstrated an improvement in symptoms.
- If adding a LAMA, ensure that the dose of the ICS component of the triple therapy is adequate.

Low-dose as-needed ICS-formoterol considerations

- Even though its *duration* of action is long, formoterol's *onset* of action is similar to albuterol, making this a safe alternative to SABA therapy alone for Step 1 therapy and as the preferred reliever in patients age 12 and older. Two different studies saw 60% or greater reduction in severe exacerbations compared with SABA alone.
- Daily low-dose ICS inhaler adherence can be a challenge for some patients, where this ICS-formoterol as needed option is middle ground between SABA as needed and daily ICS.
- The ICS-formoterol combination that was studied was budesonide-formoterol (Symbicort). Though Symbicort was the inhaler studied, Dulera is another option as the LABA in this inhaler is formoterol but dosing has been neither studied nor provided by the manufacturer.
- Other long-acting beta agonists (LABAs) cannot be substituted for formoterol-containing inhalers for this use! If a different ICS-LABA inhaler other than ICS-formoterol is the controller, use a SABA as the reliever so that a patient is not using two different ICS-LABA inhalers at once.
- Dosing: Symbicort (80 mcg budesonide/ 4.5 mcg formoterol OR 160 mcg budesonide/ 4.5 mcg formoterol) 1 puff as needed, may repeat if no relief. Maximum 12 inhalations per day.

Montelukast (Singulair) black box warning

- Though leukotriene receptor antagonists should be considered prior to initiating a biologic agent for asthma, a black box warning has been added for montelukast (Singulair) to alert prescribers to the potential for serious neuropsychiatric events including agitation, aggression, depression, sleep disturbances and suicidal thoughts and behavior.
- This new warning came in early 2020 based on case reports submitted to the FDA, observational study and a review of published literature.
- 82 cases of completed suicide associated with montelukast were identified. 45 of these cases were in patients older than 17, 19 cases were reported in patients 17 and younger and the age of the patient was not shared in 18 patients. Most of these cases did not include sufficient information to define relationship of the effects to montelukast.
- Prescribers should evaluate the risks and benefits of utilizing montelukast, and if prescribed the patients should be counseled about the risk of neuropsychiatric events. Keep in mind that leukotriene receptor antagonists such as montelukast are less effective than ICS.
- Zafirlukast (Accolate), the other leukotriene receptor antagonist, does not carry a black box warning, but does contain another precaution regarding reports of behavioral changes. Zafirlukast is prescribed far less frequently than montelukast so would be unlikely to have the same amount of data to show trends toward neuropsychiatric events that montelukast does.

Adherence and Technique

- Improving adherence to prescribed asthma therapy is an important consideration before initiating biologic treatment. Approximately 50% of asthma patients fail to take their therapy as directed at least part of the time.
- Common barriers to adherence include difficulties using the prescribed inhaler, therapy requiring multiple doses per day, cost or denial of the importance of chronic therapy to prevent exacerbations.
- Approximately 70-80% of patients are unable to use their prescribed inhaler correctly! Many of these individuals are unaware that their technique is poor, and many healthcare providers are unable to demonstrate how to utilize the inhaler properly.
- The four C's can guide a clinician in ensuring proper inhaler use:
    - **Choose** the most appropriate inhaler for the patient. If multiple inhalers are prescribed, try to use only one type of device across the multiple inhalers.
    - **Check** inhaler technique at every opportunity. Even if the patient has been using an inhaler for months or years, there is potential for deterioration in technique over time.
    - **Correct** improper technique. Using placebo inhalers will give the clinician several opportunities to correct. If the patient is still unable to use the device properly after several tries, consider another device.
    - **Confirm** proper technique utilizing various members of the health care team. In addition to nurse education, clinics with respiratory therapists and pharmacists on staff should utilize these team members to coach patients through proper technique.

Spacers

- Spacers can be utilized with pressured metered dose inhalers (pMDIs) such as Proair/Ventolin, Symbicort, Dulera, Advair HFA, and Flovent HFA.
- Benefits of spacers include:
    - Improved dose delivery. By holding the dose in suspension within a contained space, patients with difficulty coordinating their inhalation with activating the inhaler get more time to inhale the dose.
    - Reduced side effects. Spacer use with inhalers containing an ICS can reduce the risk of side effects including dysphonia and oral candidiasis. Spacers should not replace the instructions to patients to rinse and spit after each inhaled corticosteroid use.

Required Workup for Biologic Treatment

- Due to the high cost of the medications, biologics should be used only when standard asthma therapy is insufficient.
- When a biologic is to be trialed, required testing during workup includes:
    - Pulmonary Function Tests (PFTs) with FeNO
    - IgE
    - CBD with differential
    - Chest x-ray
    - Asthma control test (ACT) available at hyperlink
- See further criteria for biologic initiation compiled on Avera When to Consider a Biologic Agent for Severe Asthma guidance

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Outpatient Treatment of Asthma Exacerbations in Adults

Executive Summary: Mild to moderate asthma exacerbations can often be effectively managed outpatient, either at home or in the primary care setting, by temporarily escalating the patient's current therapy. This should include more frequent use of their reliever medication and increasing their controller (inhaled corticosteroid) dose (or adding a controller). Addition of a short course of oral corticosteroids can be considered in certain circumstances as well. These steps should be detailed in a written personal asthma action plan for the patient.

Written Asthma Action Plans

All patients with asthma should be educated regarding self-management, including skills training for effective use of inhalers, how to monitor lung function and symptoms, a written asthma action plan and regular follow-up with a health professional. A written asthma action plan should include instructions for patients to make short-term changes to their treatment in response to changes in their symptoms and/or PEF, including changes to reliever and controller medications, when and how to use oral steroids and how to access medical care.[1]

Self-Management of Asthma Exacerbations:

1. Increase usual reliever[1]:

Table 1

Low dose ICS-formoterol	Increase frequency of as-needed ICS-formoterol Maximum of 12 inhalations daily
SABA	Increase frequency of SABA use For MDI, add spacer

   a. Increasing PRN low dose ICS/formoterol doses when asthma begins to worsen reduces risk of severe exacerbation and need for oral steroids better than a SABA alone[1]
   b. ICS/formoterol ,when implemented in early stages of worsening asthma, is effective in improving symptom control and can reduce the need for steroids or hospitalization[1]
   c. Repeated SABA dosing provides temporary relief until the cause of the worsening symptoms passes or an increase in controller medication takes effect[1]

2. Increase usual controller (short-term change, 2-4 weeks)[1]:

Table 2

Maintenance and reliever ICS-formoterol	Continue maintenance ICS-formoterol and increase reliever ICS-formoterol as needed
Maintenance ICS with SABA as reliever	In adults and adolescents, quadruple ICS dose
Maintenance ICS-formoterol with SABA as reliever	Quadruple maintenance ICS-formoterol

Maintenance ICS plus other LABA with SABA as reliever	Step up to higher dose formulation of ICS plus other LABA Consider adding a separate ICS inhaler to quadruple ICS dose

3. Review response: Counsel patients to see a healthcare provider immediately if asthma suddenly worsens or continues to deteriorate despite following their asthma action plan[1,2]

Table 3

Good Response	**Incomplete Response**	**Poor Response**
No wheezing or dyspnea, PEF of ≥80% predicted or personal best	Persistent wheezing and dyspnea (tachypnea), PEF 50-79% predicted or personal best	Marked wheezing and dyspnea, PEF <50% predicted or personal best
• Contact clinician for follow-up instructions • Continue inhaled reliever every 3-4 hours for 24-48 hours PRN	• Add OCS • Continue inhaled SABA • Contact clinician urgently (this day) for further instruction	• Add OCS • Repeat inhaled SABA immediately • If distress is severe and nonresponsive to initial treatment, contact clinician and proceed to the ED

4. Oral corticosteroids (OCS)
    a. The asthma action plan should provide instructions for when and how to initiate OCS[1]
        i. Fail to respond to an increase in reliever and controller medication for 2-3 days,
        ii. Deteriorating rapidly,
        iii. PEF or FEV_1 <60% personal best or predicted value, and/or
        iv. History of sudden severe exacerbations
    b. OCS dosing[1]

Table 4

OCS: prednisone or prednisolone ***Tapering is not needed if OCS is prescribed for <2 weeks***	
Adults	40-50 mg/day (or 1 mg/kg/day) for 5-7 days *Maximum of 50 mg/day*
Children 6-11 years	1-2 mg/kg/day for 3-5 days *Maximum of 40 mg/day*

5. Antibiotics are not recommended for asthma exacerbations and should not be included in a written asthma action plan
6. Follow up within 1-2 weeks after exacerbation[1]

Management of Asthma Exacerbations in Primary Care[1]:

1. Patients presenting with mild to moderate exacerbations can be treated in a primary care setting – perform a brief focused history and relevant physical examination while promptly initiating therapy
2. Initial treatment includes the following:
    a. SABA

        i. 4-10 puffs by MDI + spacer, repeat every 20 minutes for 1 hour
        ii. No additional SABA is needed if there is adequate response to initial treatment (PEF >60-80% of predicted or personal best for 3-4 hours)
    b. OCS (initiate in office), see *Table 4* for dosing
    c. Controlled oxygen
        i. Target saturation 93-95% for adults
        ii. Target saturation 94-98% for children 6-11 years
3. If the patient is improving (not needing SABA, PEF improving, oxygen saturation >94% on room air) and their resources at home are adequate, the patient may be sent home and manage medications as follows:
    a. Continue reliever as needed
    b. Short course of OCS as described in *Table 4*
    c. Check inhaler technique and adherence
    d. Controller medication:
        i. Patients already on a controller should increase the dose as described in *Table 2* for the next 2-4 weeks
        ii. Patients not on a controller should be started on regular ICS-containing therapy
4. Antibiotics are not recommended for treatment of asthma exacerbations, only initiate antibiotics if there is strong evidence for lung infection (e.g., fever and purulent sputum)
5. Follow up within 2-7 days to assess resolution of exacerbation symptoms

Follow up after outpatient management of exacerbation[1]:

1. Assess for resolution of exacerbation symptoms and risk factors for exacerbations
2. Review the action plan to determine if it met the patient's needs and revise if needed
3. Controller can go back to normal about 2-4 weeks after the exacerbation unless history suggests long-term poorly controlled asthma caused the exacerbation
4. Check inhaler technique and adherence before stepping up therapy
5. Consider stepping up treatment depending on cause of exacerbation

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