Treatment of Acute Asthma Exacerbations in Adults in the Primary Care or Urgent Care Setting Clinical Practice Guideline

> *"These guidelines are provided to assist physicians and other clinicians in making decisions regarding the care of their patients. They are not a substitute for individual judgment brought to each clinical situation by the patient's primary care provider-in collaboration with the patient. As with all clinical reference resources, they reflect the best understanding of the science of medicine at the time of publication but should be used with the clear understanding that continued research may result in new knowledge and recommendations".*

Background:

Asthma is a chronic inflammatory condition of the airways affecting more than 20 million adults in the U.S.[1] 40% of adults with asthma will have an asthma attack each year, 28% will have an ED visit, and 2.6% will be hospitalized. In 2021, 3372 adults died from asthma, and the death rate was 2.5 times higher in blacks than in whites.[1] The aim of this guideline is to review the diagnosis, treatment, and prevention of acute asthma exacerbations in the outpatient setting.

Various sources are cited, but the major sources for this guideline are the 2007 National Heart, Lung and Blood Institute's National Asthma Education and Prevention Program (NAEPP), Expert Panel 3: Guidelines for the Diagnosis and Management of Asthma, the 2020 Focused Updates to the Asthma Management Guidelines from NAEPP and the 2023 Global Initiative for Asthma (GINA) Report, Global Strategy for Asthma Prevention and Management.

The MedStar Health Ambulatory Best Practices Committee endorses the Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention 2023 report. https://ginasthma.org/

Definitions/Clarifications:

- Asthma Action Plan: A written treatment plan for home use, based on symptoms and PEF.
- FEV_1: Forced expiratory volume in 1 second.
- PEF: Peak expiratory flow
- SABA: Short-acting beta agonist
- LABA: Long-acting beta agonist
- ICS: Inhaled corticosteroid
- MDI: Metered-dose inhaler ("puffer")

- An asthma exacerbation is an acute or subacute episode of progressively worsening asthma symptoms, namely shortness of breath, cough, wheeze, chest tightness or a combination thereof that corresponds with an objectively measurable decrease in expiratory airflow (FEV_1 or PEF).[4] This represents a change from the patient's usual status that is sufficient enough to require a change in treatment.[12]
- These recommendations apply to patients with an existing diagnosis of asthma as well as to those with an initial presentation of reactive airways disease who may ultimately be diagnosed with asthma.
- This guideline applies to the outpatient office or urgent care setting.
- As with all facets of medicine, guidelines should inform and guide clinical judgment, but all patients and cases must be considered on an individual basis.
- Specific dosages of medications will be in a table format near the end of the guideline.

Pathogenesis:

Asthma is a complex pathogenic process that is a combination of chronic inflammation of the airways and bronchial smooth muscle constriction leading to airway obstruction. Histologically, various cell types (neutrophils, eosinophils, lymphocytes, macrophages) are responsible for the inflammatory changes depending on the chronicity, provoking factors, age and individual genetic differences.[2] In some patients, the chronic inflammation leads to airway remodeling over time.

Generally speaking, exacerbations are thought to involve similar pathophysiology as chronic asthma. It was historically thought of as a simple worsening or loss of control. Some more recent evidence suggests that the pathophysiology of acute exacerbations may not be identical. This is based on specific histologic patterns. It is also suggested by the fact that PEF values are often markedly different during acute exacerbations compared to chronically very poorly controlled asthma, suggesting a possible difference in how the $beta_2$-adrenoreceptor functions during acute exacerbation.[2]

Diagnosis:

The diagnosis of acute asthma exacerbation is a clinical diagnosis made in the setting of acutely worsening asthma symptoms (SOB, chest tightness, wheezing, cough). Objective measurements such as hypoxemia, hypercapnia, decreased FEV_1, decreased PEF and specific physical exam findings can help to *confirm* the diagnosis and *qualify the severity* of the exacerbation.

GINA notes an FDA safety communication under conditions of hypoxemia, oxygen saturation may be overestimated by pulse oximeters in people with dark skin color.
https://www.fda.gov/medical-devices/safety-communications/pulse-oximeter-accuracy-and-limitations-fda-safety-communication

As always, a differential diagnosis of other possible conditions must be considered; the following are a few examples but should not be considered an exhaustive differential:

- Foreign body aspiration/upper airway obstruction
- Chemical exposure/pneumonitis
- Bacterial pneumonia (does not exclude concomitant asthma)
- Vocal cord dysfunction
- Tracheomalacia
- Pulmonary embolism
- Congestive heart failure

Assessment of Severity/Triage of the Asthma Exacerbation:

Table 1[4,5]: Assessing the Severity of Exacerbations-from NHLBI EPR3 (Fig 5-1).

	Symptoms and Signs	Initial PEF (or FEV_1)	Clinical Course
Mild	Dyspnea only with activity (assess tachypnea in young children)	PEF ≥70 percent predicted or personal best	■ Usually cared for at home ■ Prompt relief with inhaled SABA ■ Possible short course of oral systemic corticosteroids
Moderate	Dyspnea interferes with or limits usual activity	PEF 40–69 percent predicted or personal best	■ Usually requires office or ED visit ■ Relief from frequent inhaled SABA ■ Oral systemic corticosteroids; some symptoms last for 1–2 days after treatment is begun
Severe	Dyspnea at rest; interferes with conversation	PEF <40 percent predicted or personal best	■ Usually requires ED visit and likely hospitalization ■ Partial relief from frequent inhaled SABA ■ Oral systemic corticosteroids; some symptoms last for >3 days after treatment is begun ■ Adjunctive therapies are helpful
***Subset:* Life threatening**	Too dyspneic to speak; perspiring	PEF <25 percent predicted or personal best	■ Requires ED/hospitalization; possible ICU ■ Minimal or no relief from frequent inhaled SABA ■ Intravenous corticosteroids ■ Adjunctive therapies are helpful
Key: ED, emergency department; FEV_1, forced expiratory volume in 1 second; ICU, intensive care unit; PEF, peak expiratory flow; SABA, short-acting $beta_2$-agonist			

- Once the diagnosis can be made, the first question to ask is "can I safely manage this patient in the current setting?" If not, transfer to a higher level of care (ED) is indicated.

Treatment (General Principles):

- **Correction of significant hypoxemia** with supplemental oxygen; this is especially important in moderate to severe exacerbations.
- **Rapid reversal of airflow obstruction**
  - Repetitive or continuous administration of SABA
  - Early administration of systemic corticosteroids to patients who do not respond quickly and completely to SABA administration.[6]
- **Intensify therapy** to reduce the likelihood of future exacerbations.
  - Short course of systemic corticosteroid, typically 5-7 days depending on severity
  - Consideration of increasing controller medications (typically ICS and/or LABA)
  - Identifying triggers, risk factors
- **Serial measurements of lung function (FEV_1 and PEF) and reassessments** to determine response to treatment, help guide care, and determine if transfer to a higher level of care is needed.
  - Pulse oximetry is a reasonable alternative for patients in whom measurements of lung function are not feasible.
  - There are a variety of signs and symptoms scores that have been shown to be somewhat helpful in predicting outcomes and guiding care.

Home management of exacerbations:

- The cornerstone of treatment of asthma exacerbations is early recognition and early treatment initiation; **this can often most efficaciously be initiated by the patient.** It is imperative to have a written Asthma Action Plan which is reviewed with the patient at least annually by a physician or nurse[2,3]. An Adult Asthma Action Plan can be created for each patient by downloading, customizing and printing a copy from the NHLBI website: https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/asthma-action-plan-2020 or for MedStar physicians, customizing and printing "Form: Asthma Action Plan, Adult" in the Patient Education section of MedConnect.

- **All patients should:**
  - **Increase reliever medicines.**
  - **Increase controller medicines.**
  - **Review response.**

- **If PEF or FEV1 < 60% of personal best or is not improving after 48 hours: Continue reliever medicine, continue controller medicine, add prednisone, contact doctor.**

Table 2: Self-management of worsening asthma in adults with written asthma action plan based on Box 4-2 GINA 2023	
Medication	**Short term change (1-2 weeks)**
<u>Increase usual reliever</u>: **Low dose ICS/formoterol**	**Increase frequency of reliever use (maximum dose is 12 inhalations per day)**
Short-acting beta agonist (SABA)	**Increase frequency of SABA use, add spacer.** **Increase frequency of ICS-SABA (maximum dose is 12 inhalations per day)**
Combination ICS-SABA. FDA approved in 2023. Available 2024.	**2 inhalations every 4-6 hours. Max dose 12 inhalations per day.**
<u>Increase usual controller</u>: **Maintenance and reliever ICS/formoterol (MART)**	**Continue maintenance ICS/formoterol and increase reliever ICS/formoterol as needed (Maximum dose is 12 inhalations per day)**
Maintenance ICS with SABA as reliever	**Quadruple ICS dose**
Maintenance ICS/formoterol with SABA as reliever	**Quadruple maintenance ICS/formoterol (Maximum dose is 12 inhalations per day)**
Maintenance ICS/other LABA with SABA as reliever	**Step up to higher dose formulation of ICS/plus other LABA or consider adding a separate ICS inhaler to quadruple ICS dose.**
<u>Add oral corticosteroids and contact doctor; review before stopping.</u> **OCS (prednisone or prednisolone)**	**Add OCS if PEF or FEV_1 <60% personal best or predicted, or if not responding to treatment over 48 hours. AM dose preferred.** **Prednisolone 40-50 mg/day, usually for 5-7 days; no taper needed if OCS are prescribed for < 2 weeks**

Patients with the following risk factors for death from asthma should seek immediate medical attention after initial treatment (regardless of response to treatment):[4,5,10,12.]

- History of exacerbation requiring ICU or intubation
- Hospitalization or ED visit for asthma in the past year
- Hospitalization or ED visit for asthma in the past month
- Using >1 canisters of SABA per month
- Difficulty perceiving asthma symptoms or severity of exacerbations.
- Current use or recent use of steroids
- Not currently using inhaled corticosteroids.
- Those with diabetes or significant cardiac/pulmonary comorbidities
- History of food allergy
- History of psychiatric disease or psychosocial challenges
- History of poor adherence with asthma medications and/or written action plan

Treatment of acute asthma exacerbation in the outpatient setting:

- Oxygen is recommended for **most** patients.[4,7.]
    - Goal is to maintain SpO_2 levels > 90% (greater than 95% for patients who are pregnant or have concomitant heart disease).
    - SpO_2 levels should be monitored until a clear response to SABA therapy is noted.
        - When SpO_2 monitoring is not available, give oxygen to patients who:
            - have FEV_1/PEF of less than 40% predicted.
            - have coexisting heart disease.
            - are pregnant.
            - appear to be in significant distress.
- SABA treatment is recommended for **all** patients.[4]
    - Initially, up to three (3) treatments spaced every 20-30 minutes is safe.
    - In mild to moderate exacerbations, high dose MDI preferably with a valved holding chamber (spacer device) is equally effective as nebulization (4-10 puffs, can repeat every 20 min for 1 hour).
    - Nebulized SABA (with appropriate infection control procedures) is preferable for patients unable to cooperate with MDI administration and in severe exacerbations.
- Systemic corticosteroids are recommended for **most** patients. [4,6]
    - Give systemic corticosteroids to patients who have moderate to severe exacerbations. Use 40-60mg orally in a single or 2 divided doses for total of 5-7 days in adults.
    - Give systemic corticosteroids to patients who do not completely improve with initial SABA therapy.

    - Advise patients about the common adverse effects of oral glucocorticoids such as sleep disturbance, increased appetite, GI disturbance, and mood changes.
    - Intramuscular injection of a long-acting glucocorticoid formulation for example methylprednisolone 125mg can be used for patients unable to tolerate oral medications, who do not have access to oral medications or are at a high risk of medical nonadherence.
    - Disadvantages of intramuscular glucocorticoids are that the onset of action is slower than oral glucocorticoids (12 to 36 hours after administration) and the duration of effect varies from one individual to another (typically from 2 to 4 weeks). Cutaneous atrophy at the injection site and blanching of the overlying skin are also possible.
- Consider use of a SABA-Ipratropium bromide nebulizer treatment if available for moderate to severe exacerbations.[12]
- The following therapies are generally **not** recommended:[4,12.]
    - Methylxanthines
    - Inhaled epinephrine which is available over the counter and marketed directly to consumers for temporary relief of asthma symptoms have the risks of chest pain, tachycardia, elevated blood pressures, nausea/vomiting and have defective atomic devices. Especially, since epinephrine is not beta-2 receptor selective, it carries a greater risk of beta-1 and alpha adrenergic-type adverse effects, especially when used in excess doses.[14]
    - Antibiotics (unless there is compelling clinical evidence of bacterial pneumonia)
    - Aggressive hydration
    - Chest physical therapy
    - Mucolytics
    - Sedation
- Repeat assessment of clinical status as well as objective measurement of lung function (FEV_1 or PEF) is needed to assess response to therapy.

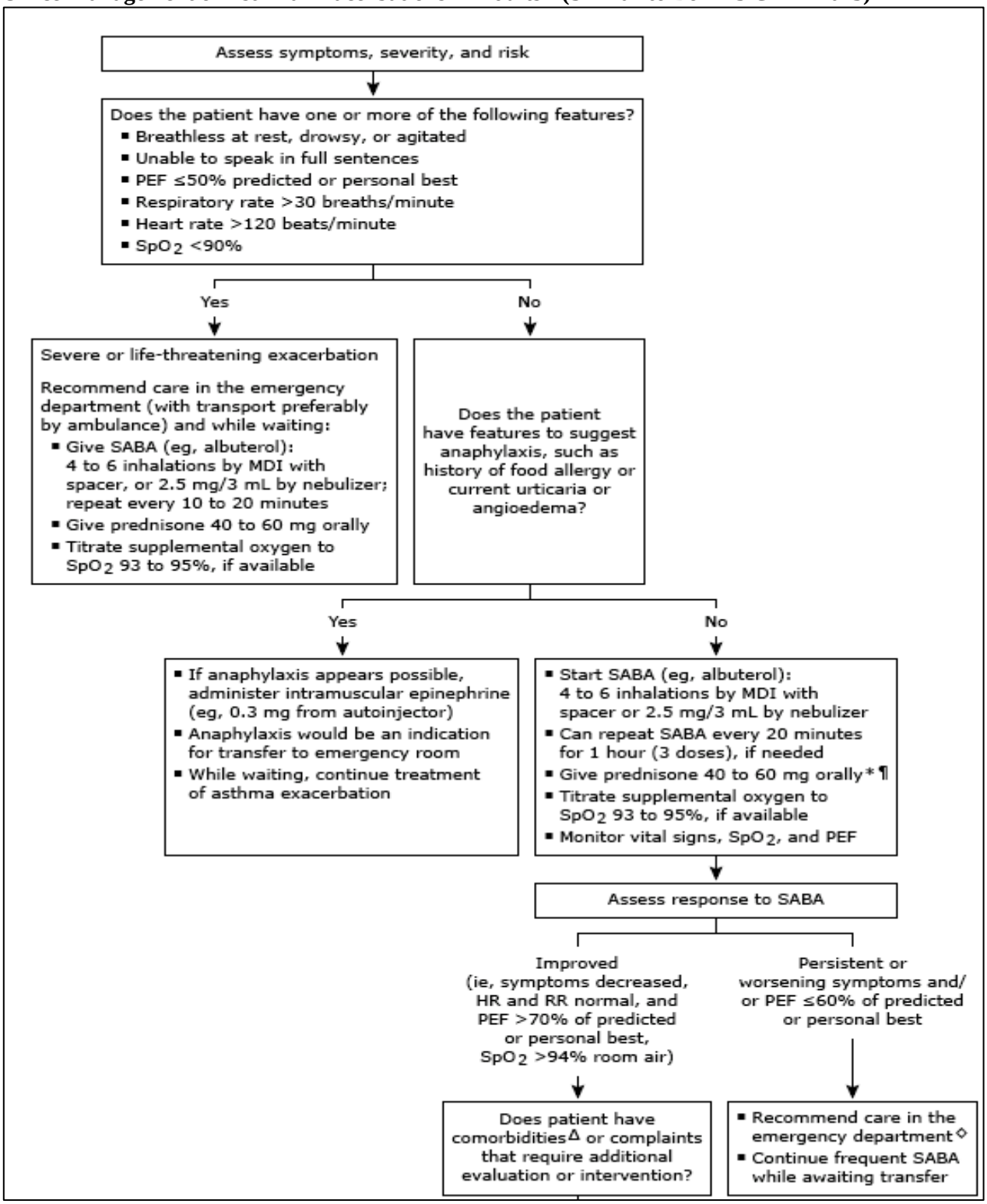
Indications against need for higher level of care:[4,7]

- Patients whose symptoms are minimal or absent and their FEV_1/PEF is ≥ 70% of predicted or of their personal best with a SpO2 >94% after initial treatment can likely manage their asthma at home unless symptoms or signs suggest a concerning comorbid condition.
    - Patients should be observed 30-60 minutes after improvement to ensure stability.
- Patients with mild symptoms and FEV_1/PEF 50-70% predicted can be considered on a case-by-case basis.
    - Patients with risk factors for death from asthma (see above) likely require higher level of care even if initial improvement occurs.
    - Individual clinical assessment is key.

Indications for transfer to higher level of care:[4]

- FEV_1/PEF ≤50% predicted/personal best or unable to perform PEF despite treatment.
- Continued moderate or severe symptoms despite treatment.
- Continued need for supplemental oxygen SpO2 <90%.
- Inability to go longer than 30-60 minutes without SABA treatment.
- Concerning physical exam findings (intercostal retractions, cyanosis, paradoxical breathing, significant tachypnea, signs of fatigue, etc.)
- Patients with significant comorbidities
- Patients with risk factors for death from asthma (see above)

Office Management of Asthma Exacerbations in Adults[11] (Similar to Box 4-3 GINA 2023)



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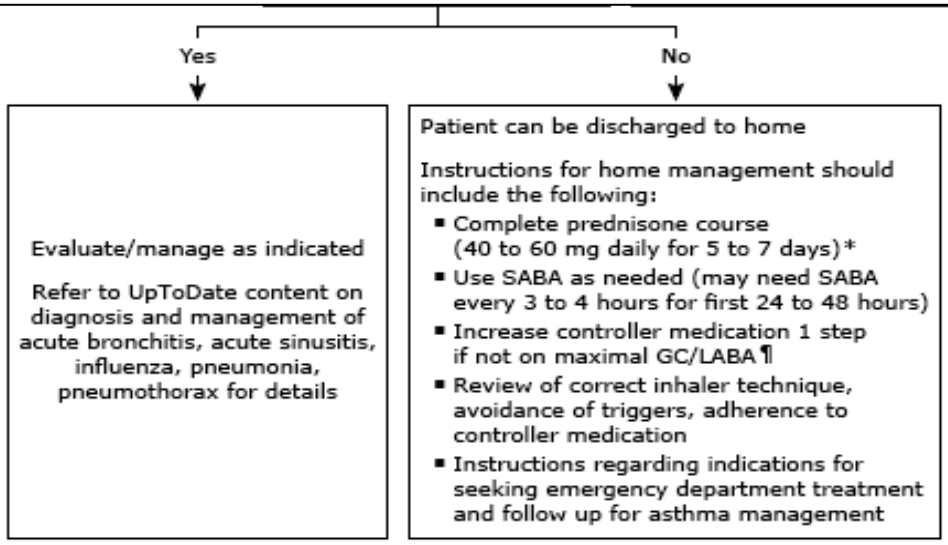

PEF: peak expiratory flow; SpO_2: pulse oxygen saturation; SABA: short-acting beta-agonist; MDI: metered dose inhaler; GC: glucocorticoid; LABA: long-acting beta-agonist.

* In a minority of patients, symptoms resolve quickly and completely with one dose of albuterol (eg, 2 to 4 inhalations or one nebulizer treatment) and PEF is ≥80% of predicted or personal best. Oral glucocorticoid is not necessary, but a step-up in controller medication may be needed.

¶ Refer to UpToDate content on asthma management or https://ginasthma.org/.

Δ Comorbid conditions that may complicate asthma exacerbation include the following:

- Acute bronchitis
- Acute bacterial sinusitis
- Heart failure; arrhythmia
- Influenza, COVID-19
- Pneumonia
- Pneumothorax

Suggestive symptoms include fever, myalgias, purulent sputum, chest pain, poor response to SABA. Refer to UpToDate content on diagnosis and management.

◇ Individuals with PEF 60-70% of predicted following initial treatment can sometimes safely continue treatment at home if their symptoms are improving, they have an asthma-safe home environment, have the necessary medications and understand their proper administration, are deemed adherent to therapy, and have ready access to emergent care if needed.

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Follow up care:

Prevention of recurrence is key:

- Regular follow up with PCP or asthma specialist[2,4]
  - Lack of PCP follow up has been shown to be a risk factor for death from asthma.[9]
- The need for continued patient education cannot be overstressed.
  - Reviewing medications individually; ensure adequate quantity and refills.
  - Reviewing (updating if necessary) asthma action plans
  - Review modifiable risk factors for exacerbations (smoking)
  - Ensure that all necessary equipment is on hand, is working and that the patient is using proper technique.
    - Peak flow meter
    - Spacer for MDI use
    - Nebulizer
  - Patient education videos (in English and in Spanish) on proper use of metered dose inhalers with and without spacers can be found at https://www.cdc.gov/asthma/inhaler_video/
  - A patient education video made by the American Lung Association on proper use of a peak flow meter can be found at https://www.youtube.com/watch?v=6oKupWgDu80
- Encourage use of a combination formoterol-corticosteroid inhaler.[12]
  - Formoterol is a LABA with a rapid onset of action comparable to albuterol. The usual dose is one to two inhalations. Can be repeated every 20 minutes up to six inhalations, if needed. The maximum daily dose is 12 inhalations. This has been referred to as Maintenance and Reliever Therapy or **MART.**
  - This combination is currently not FDA approved for asthma exacerbations.
- Consider use of a combination quick relief and corticosteroid inhaler when available.[12]
  - A combination corticosteroid-SABA inhaler has been approved by the FDA in January 2023 for adults but is not yet available. It can be used to treat an acute exacerbation like albuterol, with the advantage of administering anti-inflammatory therapy, so-called "anti-inflammatory rescue" or "AIR".
- Treatment with regular inhaled corticosteroids constitutes an important method to prevent recurrent asthma attacks after discontinuation of oral steroids and to prevent the potential decline in lung function associated with any future severe asthma exacerbation. Virtually every patient who has an asthma attack severe enough to require office-based or urgent care should receive an inhaled corticosteroid as part of their discharge medication plan.[11]
- Patients should be advised to use a spacer and to rinse their mouths after use to minimize the risks of oral candidiasis and dysphonia.[12]

- Please refer to the MedStar Guideline "Diagnosis and Management of Asthma in Adults" for list of inhaled corticosteroids. and long-term management of Asthma.
- There are several choices for inhaled corticosteroids with different costs and insurance coverage so this should be discussed with patients.
- Consider referral to an asthma specialist for patients hospitalized for asthma or re-present for acute asthma care.

Pharmacotherapy:

	How Supplied	Adult Dose	Comments	Cost*
Albuterol				
Nebulizer solution (generics only)	Nebulizer solution: 0.63mg/3mL 2.5mg/3mL 100mg/20mL Preservative free also available as 1.25mg/3mL in addition to above	Mild-moderate: 2.5mg every 20 minutes for 3 doses, then continue every 1-3 hours or taper to every 3-4 hours depending on response Moderate-severe: 2.5–5 mg every 20 minutes for 3 doses, then taper to 2.5–5 mg every 1-4 hours as tolerated, **or** 10-15 mg over 1 hour continuously for critically ill patients	May mix with ipratropium nebulizer solution.	$1.74/each

ProAir, Proventil, Ventolin and generics	HFA, MDI (90 mcg/puff)	Mild-moderate: 2-4 inhalations every 20 minutes for 3 doses, then continue every 1-3 hours or taper to every 3-4 hours depending on response. Moderate-severe: 4-10 inhalations every 20 minutes up to 3 doses, then taper to 2-4	In mild to moderate exacerbations, MDI plus VHC is as effective as nebulized therapy with appropriate administration technique and coaching by trained personnel.	Proventil HFA: $96 ProAir RespiClick: $82 ProAir Digihaler: Ventolin HFA: $27 Generic albuterol HFA: $23 200 puffs/ container
Levalbuterol				
Nebulizer solution (generics only)	Nebulizer solution: 0.31 mg/3ml 0.63 mg/3 ml 1.25 mg/3 ml 1.25 mg/0.5 ml (same strengths available as preservative free)	1.25-2.5 mg every 20 minutes for 3 doses, then 1.25-5 mg every 1-4 hours as needed	1mg levalbuterol is equivalent to 2mg of albuterol. It has not been evaluated by continuous nebulization.	$2 each
Xopenex HFA	HFA (45 mcg/puff)	Mild-moderate: 2-4 inhalations every 20 minutes up to 3 doses, then taper based on response to therapy. Moderate-severe: 4 inhalations every 20 minutes up to 3 doses, then taper or increase based on response	1mg levalbuterol is equivalent to 2mg albuterol	$74 (generic) $82 (brand) 200 puffs/container

Epinephrine				
Adrenalin and generics (1 mg/ml)	Injection solution 1 mg/ml (equivalent to 1:1,000)	0.3-0.5mg every 20 minutes up to 3 total doses if inadequate response to initial dose given IM (preferred) or SubQ	No proven advantage of systemic therapy over aerosol. Generally reserved for cases where nebulized therapy is either unavailable or clinically ineffective.	$18 per 1 ml vial (generic) $18 per 1ml vial (brand)
Ipratropium				
Nebulizer solution (generics only)	Nebulizer solution (with or without preservative) 0.5 mg/2.5 ml	0.5 mg every 20 minutes for 3 doses then hourly as needed	Should not be used as first-line therapy or as monotherapy; should only be added to SABA therapy for severe exacerbations. May mix in same nebulizer with albuterol. (The addition of ipratropium has not been shown to provide further benefit once the patient is hospitalized)	$2each
Atrovent (Brand name only	HFA, MDI (17 mcg/puff)	4-8 inhalations every 20 minutes for 3 doses then hourly as needed up to 3 hours		$550/inhaler 200 puffs / container
Combination Products				
Ipratropium with albuterol nebulization solution (generic only)	(each 3 ml contains 0.5 mg ipratropium bromide and 2.5 mg albuterol)	3 ml every 20 minutes for 3 doses, then as needed	May be used for up to 3 hours in the initial management of severe exacerbations.	$2
Ipratropium with albuterol inhaler Combivent Respimat (brand name only) Budesonide/Formoterol (Symbicort)	 Budesonide/formoterol (Symbicort) 80mcg/4.5mcg or 160mcg/4.5mcg:	4-8 puffs every 20 minutes for 3 doses, then as needed up to 3 hours. Maintenance: 2 inhalations 2x/day OFF label: 1-2 inhalations every 4hr for persistent symptoms or 2		$570 20-100 mcg/puff 120 puffs/container 160-4.5mcg/puff: $541/$40

		inhalations every 20 min for 3 doses. Max dose is 12 inhalations per day including maintenance or 6 inhalations per exacerbation.		
Albuterol/budesonide (90mcg/80mcg) (Airsupra)	2 inhalations every 4-6 hours. Max dose 12 inhalations per day.			Not available until early 2024. Price to be determined.
Corticosteroids				
Prednisone	Regular release tablets available in 1 mg, 2.5 mg. 5 mg, 10 mg, 20 mg, and 50 mg strengths. Oral solution available in 5mg/ 5ml concentration and 5 mg/ml concentrate	40-60 mg/day in 1 or 2 divided doses per day for 3-10 days until PEF reached 70% of predicted or personal best (80% for prednisolone)	For outpatient "burst", use 40-60 mg in single or 2 divided doses for total of 5-10 days in adults. prednisone 5 mg = prednisolone 5 mg = methylprednisolone 4 mg However, the same dosing was recommended for all 3 agents for simplicity per NHLBI guidelines.	40 mg dose as 2 20mg tablets: $3 Oral liquid 20 mg dose: $16 Oral concentrate 20mg dose: $21
Methylprednisolone	Tablet available in 2 mg (brand only), 4 mg, 8 mg, 16 mg, 32 mg strengths. Injection solution as sodium succinate available in 40 mg, 125 mg, 500mg and 1000mg			40 mg dose as 5 8mg tabs $10 40mg injection: $7
Prednisolone	Available as 10 mg, 15 mg, 30 mg oral disintegrating tablet; Oral solutions (varied concentrations); oral syrup 15 mg/5 ml			40 mg dose as 4 10mg tabs $58 45 mg dose oral syrup $5

- *cost = representative AWP and/or AAWP
- VHC = valved holding chamber
- PEF = peak expiratory flow
- ACT = actuations/puffs
- MDI = metered dose inhaler
- HFA = hydrofluoroalkane (propellant)

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