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

"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 nearly 25.0 million adults in the U.S.[1] 40% of adults with asthma will have an asthma attack each year, 35% will have an ED visit, and 6% will be hospitalized. In 2018, 3348 adults died from asthma, and the death rate was 2.4 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 National Heart, Lung and Blood Institute's National Asthma Education and Prevention Program, Expert Panel 3: Guidelines for the Diagnosis and Management of Asthma and the 2021 GINA report, Global Strategy for Asthma Prevention and Management.

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]

- 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 provided in 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, hypercapnea, decreased FEV_1, decreased PEF and specific physical exam findings can help to *confirm* the diagnosis and *qualify the severity* of the exacerbation.

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:

- 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.

Table 1[4,5]**: Assessing the Severity of Exacerbations**—table taken directly from NHLBI EPR3.

	Symptoms and Signs	Initial PEF (or FEV_1)	Clinical Course
Mild	Dyspnea only with activity (assess tachypnea in young children)	PEF/ $FEV_1 \geq 70$ 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/ FEV_1 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 / $FEV_1 < 40$ percent predicted or personal best	+ Usually requires ED visit and likely hospitalization + Partial relief from frequent use of 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 / $FEV_1 < 25$ 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

Treatment:

- **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 ICA 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 reliver medicines, increase controller medicines and 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.**

Medication changes for written asthma action plans	
Medication	**Short term change (1-2 weeks) for worsening asthma**
<u>Increase usual reliever</u>: **Low dose ICS/formoterol** **Short-acting beta agonist (SABA)**	 **Increase frequency of reliever use (maximum formoterol total dose of 72 mcg/day)** **Increase frequency of SABA use, add spacer**
<u>Increase usual controller</u>: **Maintenance and reliver ICS/formoterol** **Maintenance ICS with SABA as reliever** **Maintenance ICS/formoterol with SABA as reliever** **Maintenance ICS/other LABA with SABA as reliever**	 **Continue maintenance ICS/formoterol and increase reliever ICS/formoteral as needed (max formoterol total 72 mcg/day)** **Quadruple ICS dose** **Quadruple maintenance ICS/formoterol (max 72 mcg/day)** **Step up to higher dose formulation of ICS/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)**	**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]

- History of exacerbation requiring ICU or intubation
- Two or more hospitalizations for asthma in the past year
- Three or more ED visit for asthma in the past year
- Hospitalization or ED visit in the past month for asthma
- Using > 2 canisters of SABA per month
- Difficulty perceiving asthma symptoms or severity of exacerbations
- Current use or recent use of steroids
- Those with significant cardiac or pulmonary comorbidities
- History of food allergy
- History of psychiatric disease

Treatment of acute asthma exacerbation in the outpatient setting:

- 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 is equally effective as nebulization (4-10 puffs, can repeat every 20 min for 1 hr).
    - Nebulized SABA (with appropriate infection control procedures) is preferable for patients unable to cooperate with MDI administration and in severe exacerbations.

- 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 supplemental 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

- Systemic corticosteroids are recommended for **most** patients. [4,6]
    - Give systemic corticosteroids to patients who have moderate and severe exacerbations (see table 1 above)

- Give systemic corticosteroids to patients who do not completely improve with initial SABA therapy.
    - Depot intramuscular corticosteroid therapy seems to be equally efficacious when compared to oral therapy; consider this option in patients who have a risk of non-adherence to oral therapy.[4,8]

- The following therapies are generally **not** recommended:[4]
    - Methylxanthines
    - 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 FEV_1/PEF is ≥ 70% predicted with initial treatment
    - Patients should be observed 30-60 minutes after improvement to ensure continued stability
- Patients with mild symptoms and FEV_1/PEF 50-69% 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 less than 50% predicted despite treatment
- Continued moderate or severe symptoms despite treatment
- Continued need for supplemental oxygen
- 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)

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 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
- 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				
AccuNeb (only generics available)	nebulizer solution: 0.63mg/3mL 2.5mg/3mL 100mg/20mL Preservative free also available as 1.25mg/3mL in addition to above	2.5 – 5 mg every 20 minutes for 3 doses, then taper to 2.5 – 10 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.	$0.55each
ProAir, Proventil, Ventolin and generics	HFA, MDI (90 mcg/puff)	4-10 inhalations every 20 minutes up to 3 doses, then taper to 2-4 inhalations every 1-4 hours as tolerated.	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 HFA: $85 ProAir RespiClick: $80 ProAir Digihaler: $176 Ventolin HFA: $60 Generic albuterol HFA: $56-74 200 puffs/ container
Levalbuterol				
Xopenex	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 albuterol. Has not been evaluated by continuous nebulization.	$1-7 each (generic) $12 each (brand)
Xopenex HFA	HFA, MDI (45 mcg/puff)	4-8 inhalations every 20 minutes up to 3 doses, then taper based on response to therapy.	1mg levalbuterol is equivalent to 2mg albuterol	$74 (generic) $82 (brand) 200 puffs/container

Epinephrine				
Epinephrine (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				
Ipratropium (available generic only)	Nebulizer solution (with or without preservative) 0.5 mg/2.5 ml	0.5 mg every 20 minutes for 3 doses then 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)	$0.25-2.20 each
Atrovent (brand name only)	HFA, MDI (17 mcg/puff)	8 inhalations every 20 minutes as needed up to 3 hours		$513/inhaler 200 puffs / container
Combination Products				
Ipratropium with albuterol (available as generic only)	Nebulizer solution (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.	$2.31
Combivent Respimat (brand name only)	MDI / respimat inhaler (each puff contains 20 mcg ipratropium bromide and 100 mcg of albuterol	4-8 puffs every 20 minutes for 3 doses, then as needed up to 3 hours		$532 20-100 mcg/puff 120 puffs/container
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 same dosing recommended for all 3 agents for simplicity per NHLBI guidelines	40 mg dose as 2 20mg tablets: $0.40 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 regular tab 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)

References:

1. https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm
2. Abramson et al. Victorian Asthma Mortality Study Group. "Are asthma medications and management related to deaths from asthma?" *Am L Repir Crit Care Med.* 2001; 163(1):12-8
3. Rowe et al. "Corticosteroid therapy for acute asthma." *Respiratory Medicine*. 2004; 98(4):275-284
4. NHLBI EPR-2 1997
5. National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma 2007.
6. Lahn, et al. "Randomized clinical trial of intramuscular vs oral methylprednisolone in the treatment of asthma exacerbations following discharge from an emergency department." *Chest* 2004; 126(2):362-368
7. Sturdy et al. National Asthma Campaign Mortality and Severe Morbidity Group. "Deaths certified as asthma and use of medical services: a national case-control study." *Thorax* 2005;60(11):909-15,
8. https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf
9. Comparison of Inhaled Asthma Meds. Pharmacist's Letter. December 2014.
10. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf