Acute Exacerbations of Asthma & COPD

Pharmacotherapy II, February 2020

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Recommended Reading

DiPiro, Pharmacotherapy, 10th ed, pp. 355-362; 382; 393-394

Useful References

Global Strategy for Asthma Management and Prevention 2019 (*https://ginasthma.org/gina-reports/); chapters 4&6*

Global Initiative for Chronic Obstructive Lung Disease 2019 (*https://goldcopd.org/gold-reports/); chapter 5*

Prevention of acute exacerbation of COPD guideline*; Chest* 2015; 147:883-893.

Objectives

- **Know the common triggers of exacerbations, and risk factors for asthma fatalities**
- **Describe maintenance asthma and COPD pharmacotherapies that may reduce the frequency of exacerbations**
- **Be able to recognize a severe episode**
- **Recommend initial drug therapy for asthma or COPD exacerbation to be used in a home or in a health care setting**
- **Understand how to assess the response to initial therapy, and plan further therapeutic interventions**

What is an Acute Exacerbation?

- **Acute onset (usu <2 weeks)**
- **Sustained (>1 d), progressive worsening of the condition from the stable state, beyond the usual day-to-day variations for the individual (e.g., not readily reversed with short-acting bronchodilators)**
- **Occasionally presents as sudden, severe distress requiring emergency intervention**
- **Asthma: ↓ PEF or FEV1; ↑ Sx (SOB, wheeze, chest tightness, cough, noc awakenings); ↑ rescue Rx use**
- **COPD: ↑ sputum, dyspnea, cough; worsened ventilation/gas exchange**

Characteristics of Acute Exacerbations of Asthma & COPD

	Asthma	*COPD*
Frequency	0-1 per year	1-2 per year
Triggers	Viruses, allergens, smoke	Viruses, bacteria, smoke
Presentation	Dyspnea, ↑ obstruction	↑Dyspnea & sputum, worsening ABG's
Secretions	Mucus plugs	↑Volume, ↑purulence of sputum
Fatalities	Rare	Common

Prevention of Acute Exacerbations of Asthma & COPD

Asthma		*COPD*
Yes!!!	***Inhaled Steroids***	Severe; Freq. exac; ↑Eos
No!!! (mono Rx)	***Long-acting β agonist***	Yes
Yes	***ICS + LABA***	Yes
Yes (mono Rx), but <ICS	***Leukotriene modifiers***	Not studied
Yes, added to ICS±LABA	***Anti-muscarinic***	Yes (mono & combo Rx)
In severe allergic asthma	***ICS + anti-IgE mAb***	Not studied
Not studied	***Roflumilast***	*Severe; Freq. Exac.*
Yes (for severe, freq exac)	***Macrolide antibiotics***	Yes, for poorly-controlled
Yes, per biomarkers	***Biologics***	Yes, for ↑Eos
Influenza	***Vaccines (recommended)***	Influenza, Pneumococcal
Yes	***Smoking cessation***	Yes!!!

Asthma- Importance of Exacerbations

- **Account for a large % of ER visits, and the most frequent cause of hospitalization for children**
- **Repeated severe exacerbations are associated with accelerated loss of airway function**
- **Many emergency cases probably could be avoided with optimal asthma maintenance therapy**
- **Rate of fatal asthma has *decreased* since mid-90's, but still higher than in mid-70's**

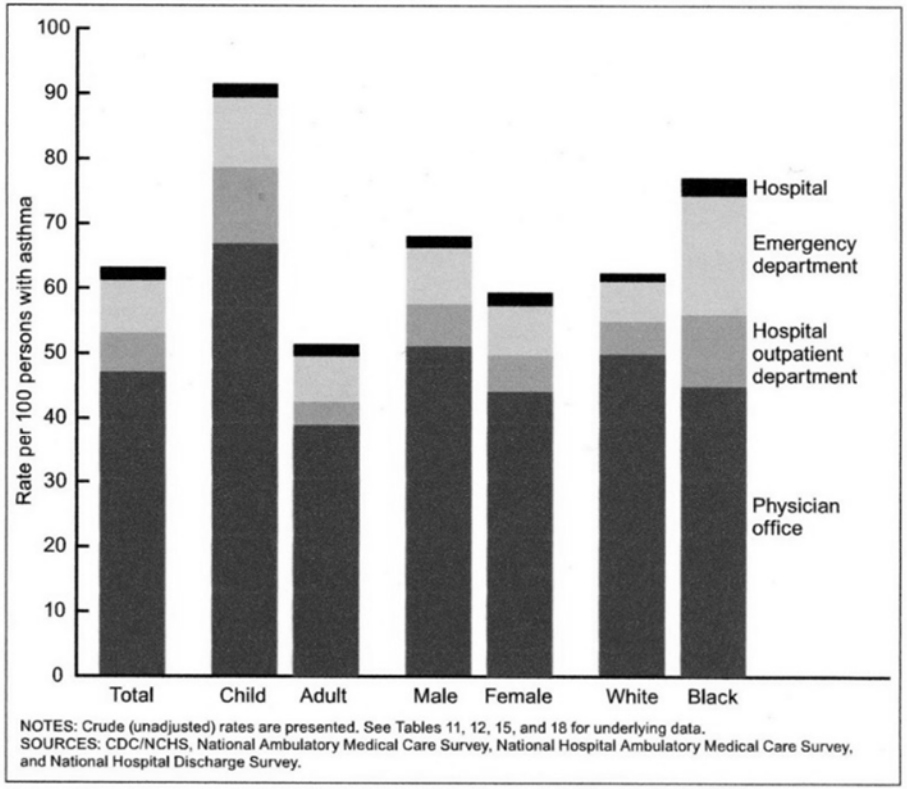
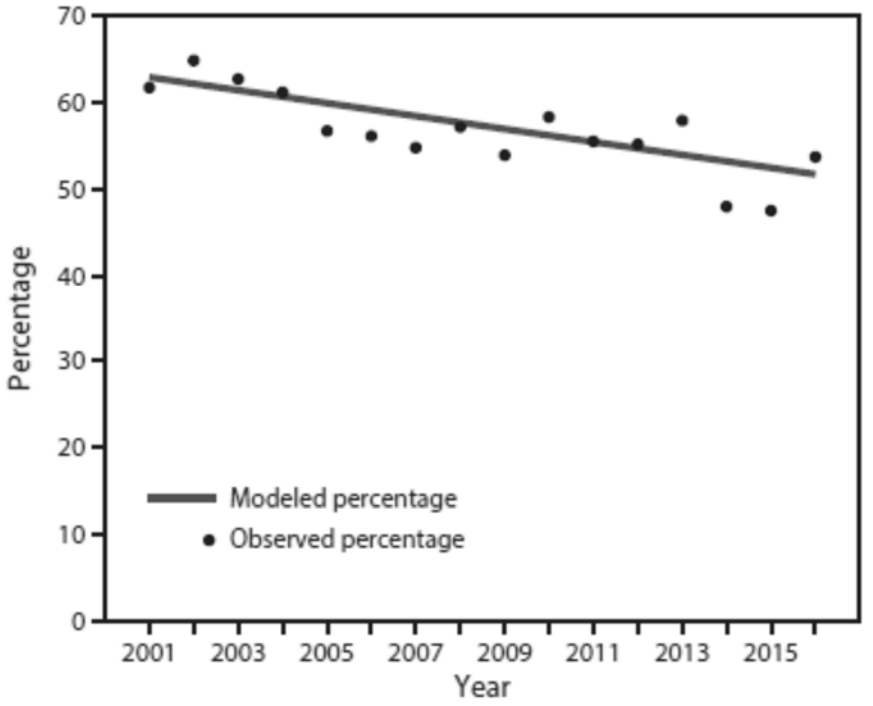


Figure 30. Asthma physician office visit rates, hospital outpatient department visit rates, emergency department visit rates, and hospitalization rates (risk-based), by age, sex, and race: United States, average annual 2007–2009

CDC 2012

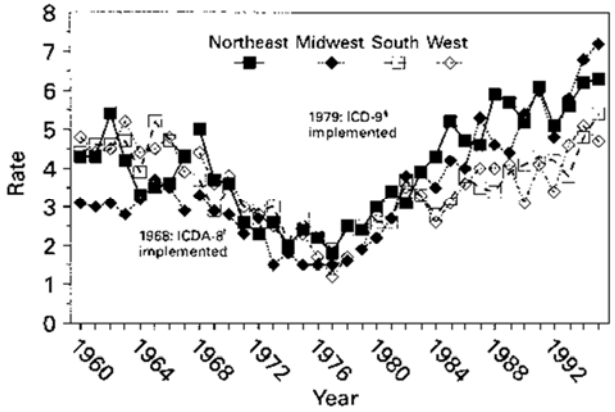
FIGURE. Percentage of asthma attacks among children aged 0–17 years with current asthma, by year — National Health Interview Survey, 2001–2016



MMWR 2018

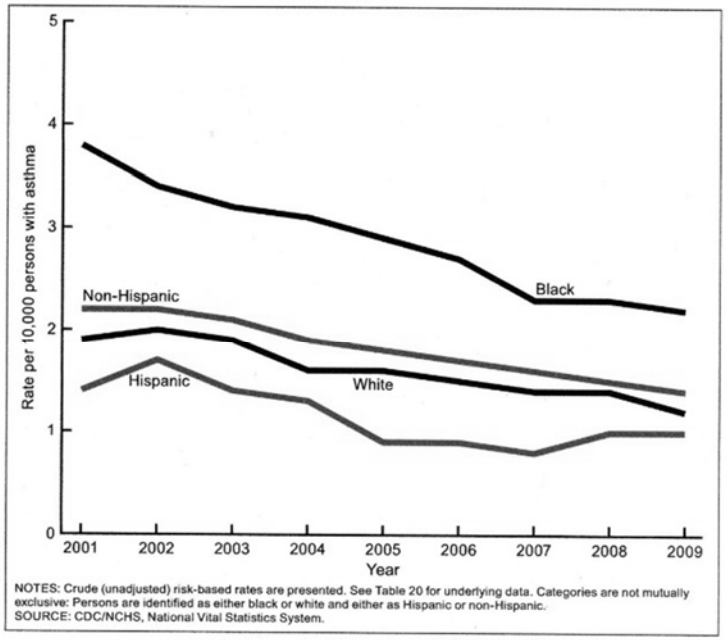
Deaths Due to Asthma

FIGURE 11. Rates* of deaths for asthma as the underlying cause of death, among persons aged 5–34 years, by region and year — United States, Underlying Cause of Death dataset, 1960–1995



*Per 1,000,000 population.
† *International Classification of Disease, Eighth Revision (Adapted).*
§ *International Classification of Diseases, Ninth Revision.*

MMWR 24 Apr 1998



NOTES: Crude (unadjusted) risk-based rates are presented. See Table 20 for underlying data. Categories are not mutually exclusive: Persons are identified as either black or white and either as Hispanic or non-Hispanic.
SOURCE: CDC/NCHS, National Vital Statistics System.

Figure 24. Asthma death rates (risk-based), by race and ethnicity: United States, 2001–2009

CDC 2012

Risk Factors for Asthma Fatalities

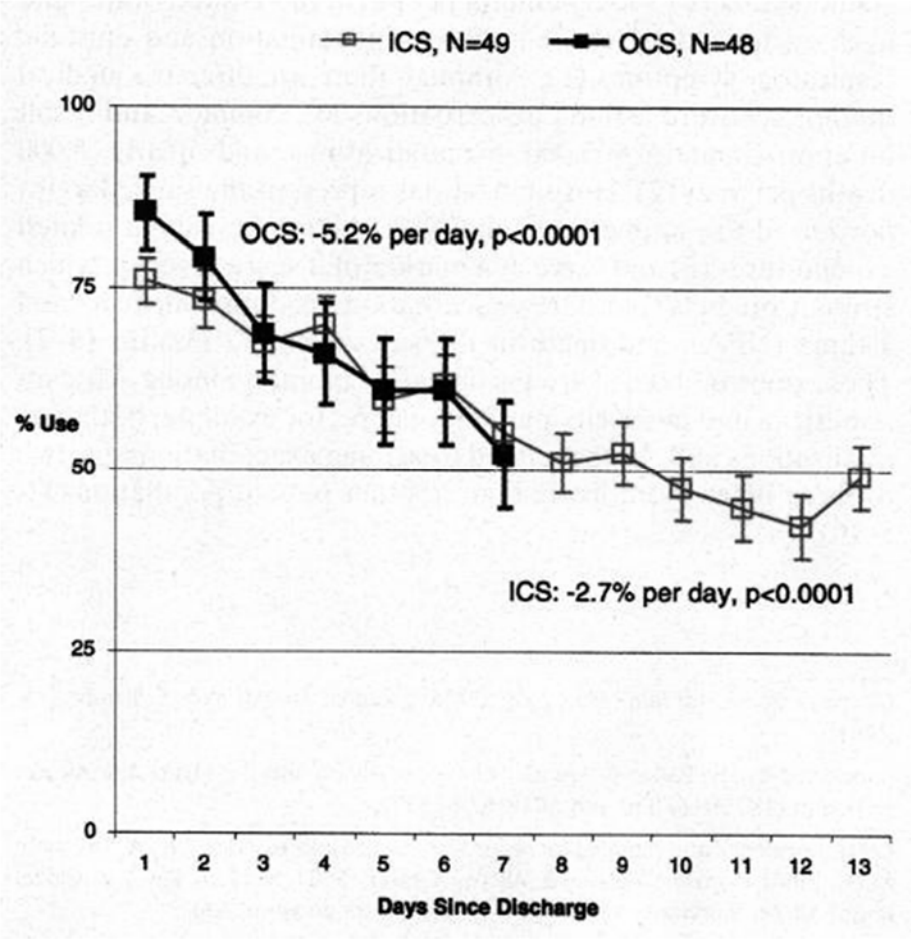
- History of near-fatal asthma requiring intubation & mechanical ventilation
- Hospitalization or ED visit for asthma in the past year
- Currently using or recent use of oral corticosteroid Rx
- Not currently using inhaled corticosteroid Rx
- Over-use of SABAs (e.g. >one canister/month)
- History of psychiatric disease or psychosocial problems
- Poor adherence with asthma controller medications
- Poor adherence with, or lack of, a written asthma action plan
- Food allergy + asthma

GINA 2018

Most Severe Exacerbations Can Be Prevented

- **Inhaled Corticosteroid (ICS) Therapy**
  - **ICS treatment reduces the number of exacerbations**
  - **Combination Rx of ICS + long-acting beta agonist further reduces exacerbations**
  - **Withdrawal of ICS Rx precipitates an exacerbation within days in many asthmatics**
  - **Poor adherence is common**
- **Education, Monitoring, Action Plan**
  - **Enrollment in studies always improves asthma control**
  - **Early detection of and intervention for exacerbations to avoid severe episode and hospitalization**

Corticosteroid Use after Hospital Discharge among High-risk Adults with Asthma

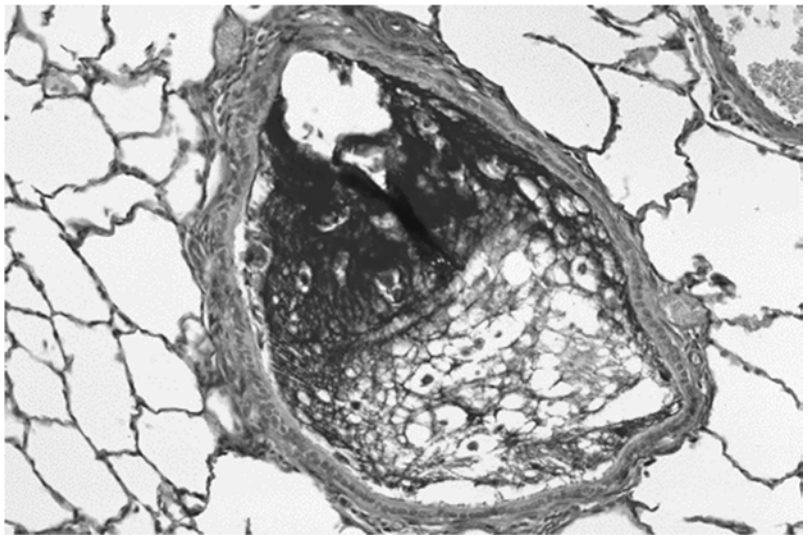


Krishnan, *AJRCCM* 2004

Pathophysiology and Presentation

- **Usually progressively worsening airway obstruction over several days**
- **Airway obstruction due to airway wall inflammation/edema, mucus plugging, smooth muscle contraction**
- **Hyperinflation due to air trapping**
- **Hypoxia due to $\dot{V}/Q$ mismatch**
- **Hyperventilation, progressing to hypoventilation**

Mucus & Luminal Liquid

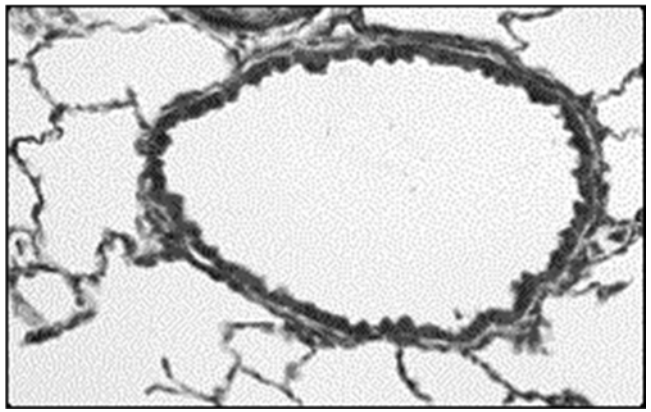


Mechanical occlusion of small airway due to mucus plug

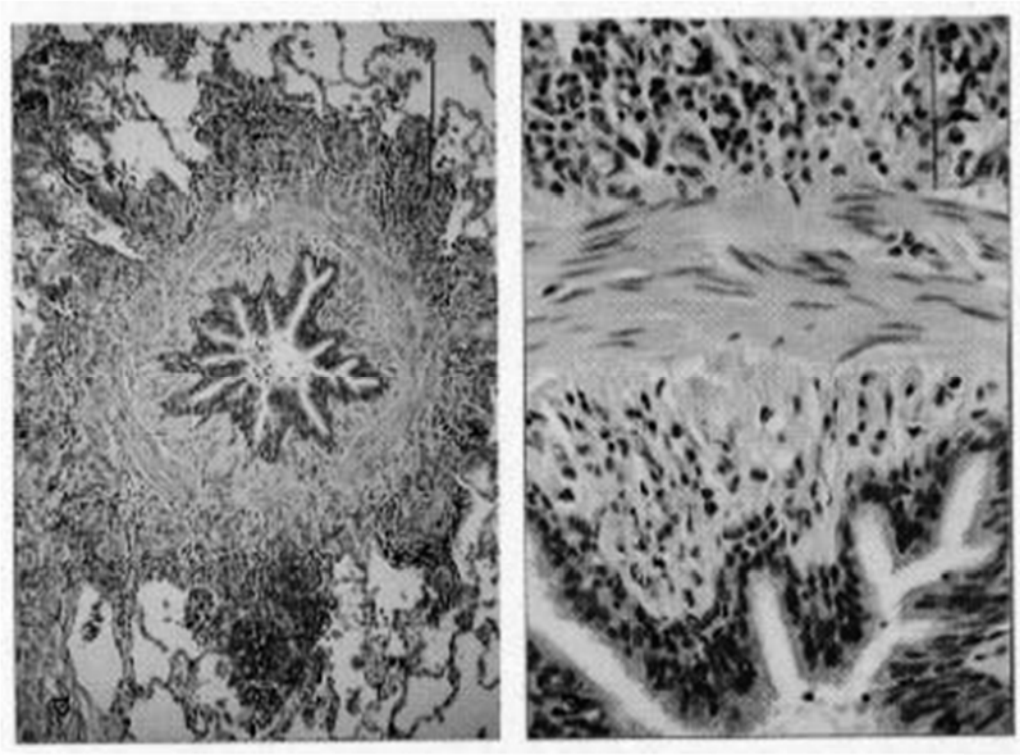
medlib.med.utah.edu/WebPath/LUNGHTML/LUNGIDX.html

Large mucus plug expelled from airway of patient with asthma exacerbation

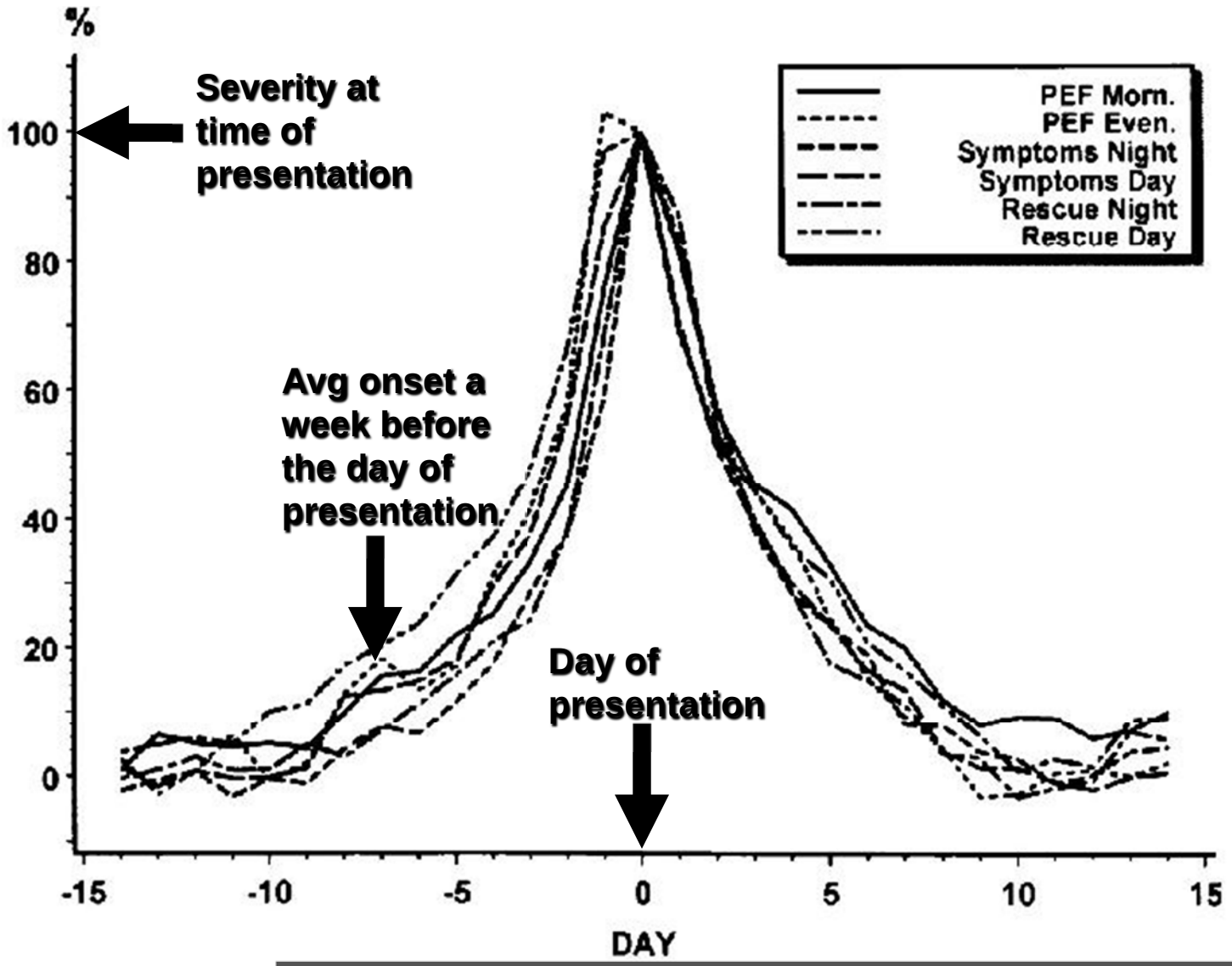
Airway Inflammation and Narrowing in Asthma Exacerbation



Normal small airway



Airway from fatal asthma exacerbation
(Saetta, 1999)

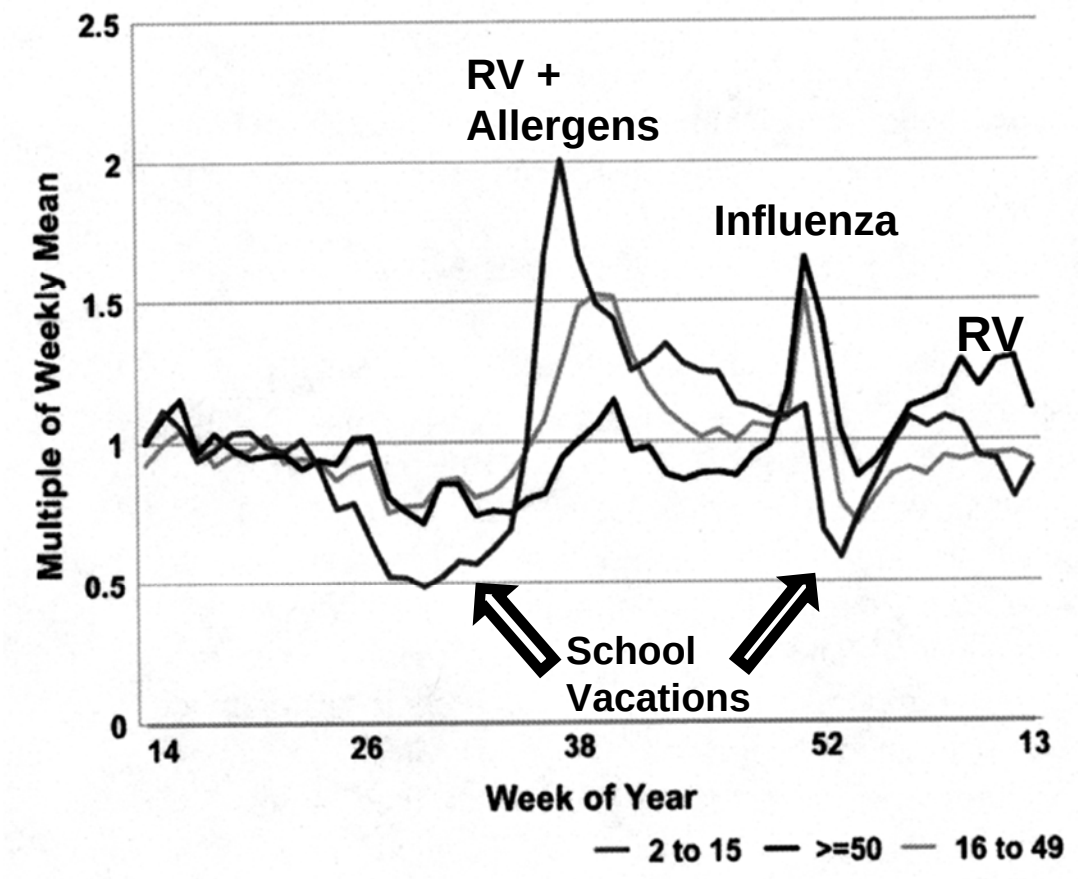


Tattersfield, Am J Resp Crit Care Med 1999; 160:594-599

Triggers of Asthma Exacerbation

- **Withdrawal of inhaled corticosteroid Rx**
- **Respiratory viral illness- especially *rhinovirus***
- **Allergic reactions**
- **Drug-induced- aspirin; β_2-antagonists**
- **Irritants- smoke, pollutants, chemicals**
- **Sinusitis**

Colds, Allergies and Asthma Exacerbations



Sears, JACI 2008

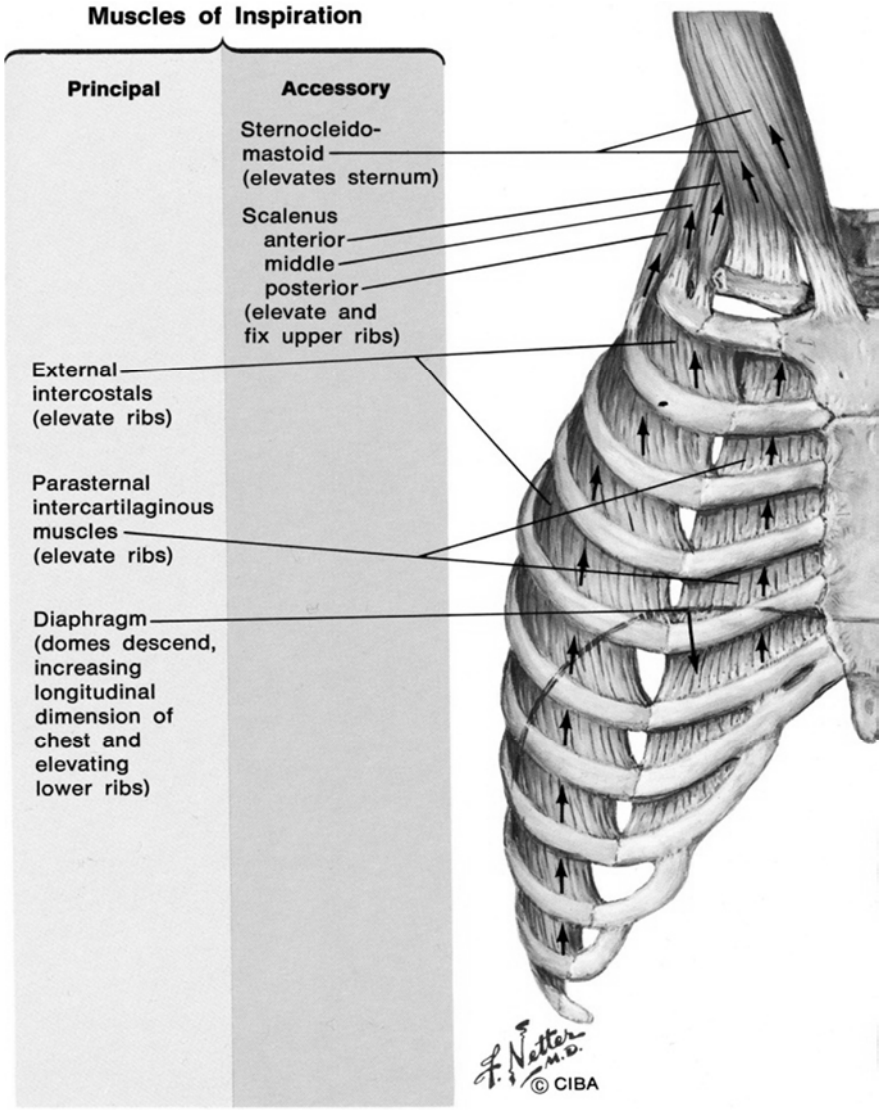
Assessment of Severity

(GINA 2019, Box 4-4)

Findings in adults with severe asthma:

- **Breathless, agitated, a few words/breath**
- **Sits hunched forward**
- **R >30, accessory muscles, HR >120**
- **PEF <50% predicted or personal best**
- **SpO_2 <90% on room air**
- **PaO_2 <60 mmHg, $PaCO_2$ >42 mmHg**

Accessory Muscles for Inspiration



Treatment of Acute Asthma Exacerbation

Target	***Treatment***
• Smooth muscle tone	• Short-acting bronchodilators
• Inflammation, edema, mucus plugging	• Systemic corticosteroids
• Hypoxia	• Oxygen
• Refractory obstruction	• $MgSO_4$; Heliox
• Ventilatory failure	• Intubation & Mechanical Ventilation

Home Management

- **Early management of an exacerbation is important: recognition of early signs; written intervention plan; communication**
- **Using ICS/Formoterol as Rescue Rx may help abort a developing exacerbation**
- **ED or 911 call if poor response to Rescue Rx**
- **Special attention to patients with risk factors for fatal asthma**

Self-Management of Worsening Asthma Using a Written Asthma Action Plan

Medication Options	*Short-term change (1-2 wks)*
Increase Usual Reliever:	
SABA	– **↑SABA as needed**
Low dose ICS/Formoterol	– **↑ICS/F, up to max F 72 mcg/d**
Increase Usual Controller:	
ICS/Formoterol	– **Max formoterol of 72 mcg/d**
ICS + SABA	– **↑ICS to high dose; ↑SABA prn**
ICS/Formoterol + SABA	– **Up to max F 72 mcg/d + SABA prn**
ICS/Salmeterol + add ICS + SABA	– **Maint dose of ICS/Salmet + additional ICS to high total dose + SABA prn**
Contact MD/add oral CS	– **p.o. prednisone, max 40-50 mg/d if inadequate response to inhaled Rx**

GINA 2018, Box 4-2

Management of Asthma Exacerbation in ED or Clinic

- **Initial assessment, then maximal bronchodilation (short-acting beta agonist ± ipratropium via nebulizer or MDI)**
- **Also Rx with O_2 to keep SpO_2 93-95%**
- **Begin systemic steroid Rx in antiinflammatory doses (e.g. prednisone 50 mg/d in adults; 1-2 mg/kg in children)**
- **Reassessment- response to 1st hr of bronchodilators will guide next step of therapy**
- **~3/4 will stabilize within a few hrs, and can go home (of those ~7% will return with relapse <1 week)**
- **Adjunct therapies ($MgSO_4$, heliox) if poor response to bronchodilators**

Adult ED Asthma Exacerbation Algorithm (Age 18 years or older)

UW Health

Last reviewed/revised: 07/2015
Contact CCKM for revisions.
Asthma – Pediatric/Adult – Inpatient/Ambulatory Guideline

Adult patient presentation to ED with asthma exacerbation
RT perform spirometry (if patient able)

Does patient have any of the following?*
- FEV1 or PEF < 40% or unable to perform spirometry due to work of breathing?
- Diffuse wheezes or poor air movement without wheezes?
- Breathless at rest/agitated or confused?
- In need of O_2 to keep SpO_2 > 92%?

No

Mild Exacerbation
STANDARD DOSE THERAPY
- RT order and give albuterol 5 mg via nebulizer x1.
- RT order and give ipratropium bromide 500 mcg via nebulizer x1 (if using albuterol at home > q2-4 hours).
- Administer O_2 to maintain $SpO_2 \geq 92\%$
- Oral corticosteroids per ED provider

Yes

Moderate or Severe Exacerbation
HIGH DOSE THERAPY
- RT order and give albuterol 5 mg Q20 min x3 in 1st hour via nebulizer
- RT order and give ipratropium bromide 500 mcg Q20 min x3 via nebulizer
- Administer O_2 to maintain $SpO_2 \geq 92\%$
- Oral corticosteroids per ED provider
- Consider $EtCO_2$ or arterial blood gas per ED provider

RT assess response to intervention (including spirometry)

Good Response
Patient exhibits at least one of the following:
- FEV1 or PEF > 70%
- No distress, normal exam
- Response sustained for > 60 min.

RT notify ED provider

Initiate Discharge Planning

Incomplete Response
Patient exhibits at least one of the following:
- FEV1 or PEF = 40-69%
- Mild or moderate symptoms*

RT notify ED provider

RT order and give albuterol via MDI with spacer x8 puffs or 5 mg Q20 min. x2 via nebulizer.
MDI therapy is the preferred delivery method. If the patient is unable to perform MDI therapy adequately, give treatments via nebulizer.

RT assess response to intervention (including spirometry)

Good Response
Patient exhibits at least one of the following:
- FEV1 or PEF > 70%
- No distress, normal exam
- Response sustained for > 60 min.

RT notify ED provider

Incomplete or Poor Response
Patient exhibits at least one of the following:
- FEV1 or PEF < 70%
- PCO2 > 42 mmHg
- Mild, moderate, or severe symptoms*
- Significant distress

RT notify ED provider

Poor Response
Patient exhibits at least one of the following:
- FEV1 or PEF < 40%
- PCO2 > 42 mmHg
- Severe symptoms*
- Significant distress

RT notify ED provider

RT order and give albuterol continuous at 0.5 mg/kg over 1 hour (up to 15 mg/hour) via nebulizer

- Administer O_2 to maintain $SpO_2 \geq 92\%$
- IVF per ED provider
- ED provider to consider possible intubation and ventilation or adjunctive therapies: Heliox (if FiO_2 < 50%); BiPAP; HFNC; Magnesium sulfate 50-75 mg/kg (max 2 g) over 20 min

Continue Reassessment and Admission Planning
RT notify ED provider

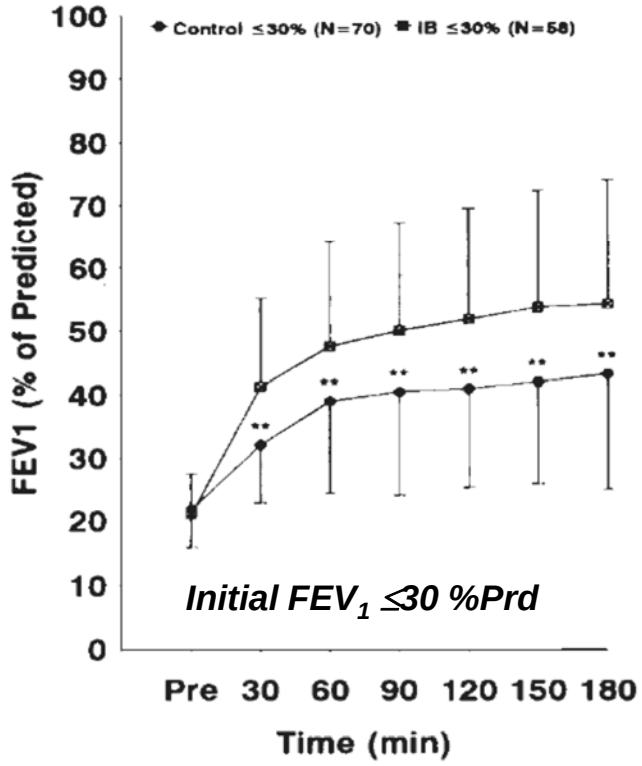
Admit to Hospital

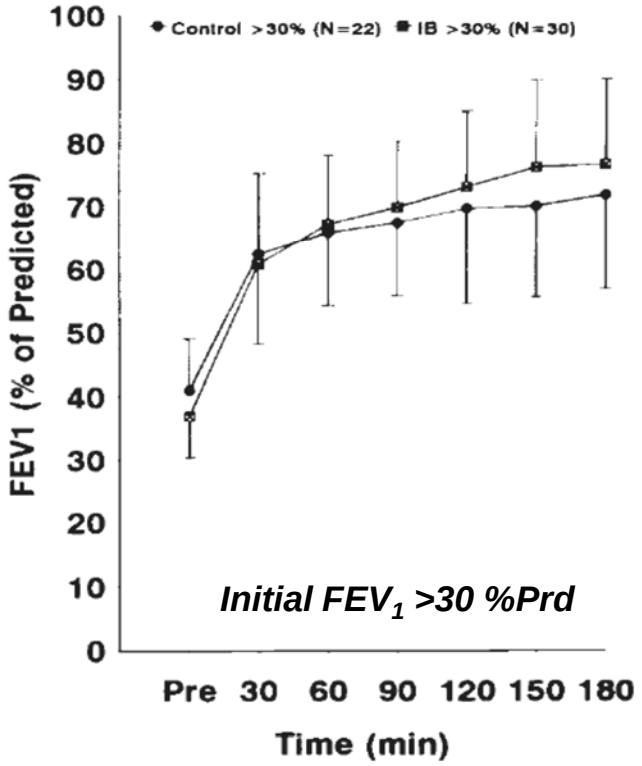
Maximal Bronchodilation

recommendations for choice of drugs

- **Inhaled short-acting β_2 agonist Rx is effective**
  -no advantage of *parenteral* terbutaline or epinephrine - use only if inhalation route not possible
- **Similar efficacy for albuterol vs levalbuterol**
- **Initial regimen 4-10 puffs MDI, repeated q20 min for 1 hr**
- **LABAs/LAMAs: avoid for acute exacerbation**
  -*Formoterol* has been used for acute bronchodilation, but avoid *salmeterol* in acute obstruction
- **Adding inhaled ipratropium to SABA:**
  -Improved therapeutic effect if *severe* obstruction initially
  -Greater reversal of obstruction and reduced %hospitalization in both adults & children
  -Discontinue after initial bronchodilation is completed

Albuterol ± Ipratropium





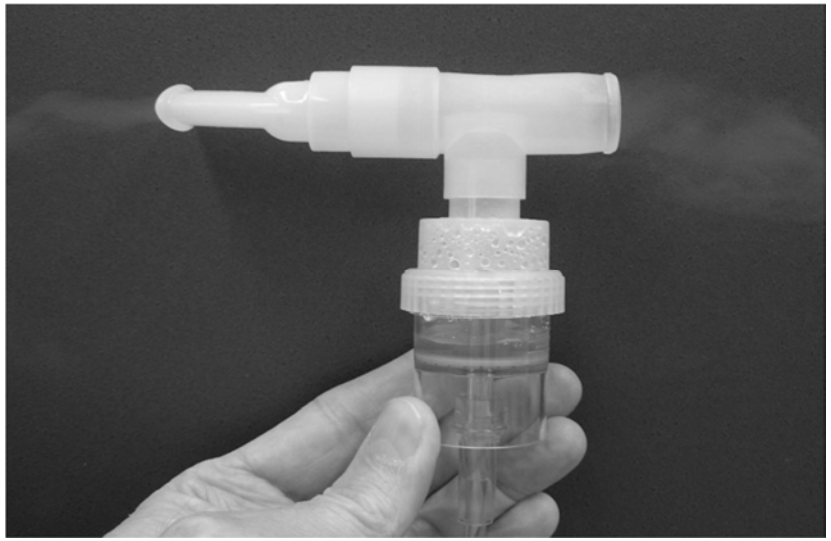
Rodrigo, AJRCCM 2000;161:1862

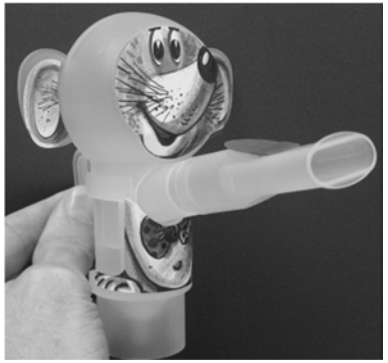
How Best to Administer Inhaled Bronchodilators?

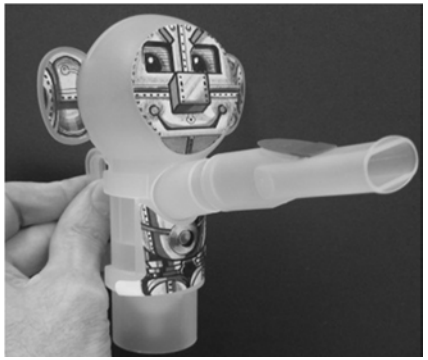
- **If tachypnea or hyperinflation present, avoid unmodified MDI**
- **MDI with valved holding chamber (MDI-VHC) is more forgiving re coordination & breathing pattern (note DPIs & Respimat will not work with VHC)**
- **Nebulizer takes 10-20 min to deliver a dose, but allows tidal breathing & can connect O_2 to neb.**
- **Can combine albuterol + ipratropium in nebulizer**
- **"Dose" is the amount placed in the nebulizer, or discharged by the MDI- unpredictable deposition in airways; therefore use generous amounts to achieve maximal effect**

Valved Holding Chambers for MDI’s

Nebulizers







How Best to Administer Inhaled Bronchodilators? (cont'd)

Adults

- Similar efficacy of MDI-VHC vs intermittent nebulization
- Continuous vs intermittent nebs reduced %hospitalization, improved FEV_1 & PEF; severe cases more likely to benefit

Young Children

- Less cooperative with nebulizer therapy
- Better efficacy using MDI-VHC

Oral & Inhaled Corticosteroids

- **Severe exacerbations should be treated with systemic steroids**
- **Onset of therapeutic effect in 6-12 hr**
- **Typically 3-7 days (3-5 d in children) systemic steroid Rx needed; in children dexamethasone 0.6 mg/kg (12 mg max) X2 days works well**
- **Resume inhaled steroids when able to breathe more normally- combined oral + ICS ok**
- **Not necessary to taper systemic steroids if used <3 wks and patient is using inhaled steroid**

Adjunctive Therapies for Poorly-Responding Asthma Exacerbations

- **i.v. $MgSO_4$ (~2 g over 20 min in adults)- may improve obstruction when added to std Rx in those with FEV_1<30% predicted**
- **Heliox- 60-80% He mixed with O_2 reduces turbulence of gas flow- may improve work of breathing and distribution of nebulized drugs**
- **Mechanical ventilation- necessary in ~2% of asthma exacerbations**

Therapies *Not* Recommended for Acute Asthma

- **Empiric antimicrobial therapy**
  - **Only if clinical evidence of bacterial infection**
- **Xanthines**
  - **Aminophylline or theophylline adds little efficacy and has potentially serious toxicity**
- **Excessive fluid therapy**
  - **Rx dehydration, but do not “push” fluids**
- **Mucolytic agents**
  - **Inhaled Acetylcysteine ineffective & may irritate airways**
- **Sedative, opiate or antianxiety agents**
  - **May reduce ventilatory drive**

FIGURE 5–8. CHECKLIST FOR HOSPITAL DISCHARGE OF PATIENTS WHO HAVE ASTHMA

Intervention	Dose/Timing	Education/Advice	M.D./R.N. Initials
Inhaled medications (e.g., MDI with valved holding chamber (VHC or spacer); nebulizer)	Select agent, dose, and frequency (e.g., albuterol)	■ Teach purpose ■ Teach and check technique ■ For MDIs, emphasize the importance of VHC or spacer	
SABA	2–6 puffs every 3–4 hours as needed		
Corticosteroids	Medium dose		
Oral medications	Select agent, dose, and frequency (e.g., prednisone 50 mg qd for 5 days)	■ Teach purpose ■ Teach side effects	
Peak flow meter	For selected patients: measure a.m. and p.m. PEF, and record best of three tries each time	■ Teach purpose ■ Teach technique ■ Distribute peak flow diary	
Followup visit	Make appointment for followup care with primary clinician or asthma specialist	Advise patient (or caregiver) of date, time, and location of appointment, ideally within 7 days of hospital discharge	
Action plan	Before or at discharge	Instruct patient (or caregiver) on simple plan for actions to be taken when symptoms, signs, or PEF values suggest airflow obstruction	

Key: MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting $beta_2$-agonist.

NAEPP 2007

COPD Exacerbations:
Signs of Severity

- **Use of accessory muscles**
- **Paradoxical chest wall movements**
- **Worsening or new hypoxia**
- **Development of peripheral edema**
- **Hemodynamic instability**
- **Deteriorated mental status**

GOLD 2016

COPD- Management of Exacerbations

- **Oxygen- to maintain SpO_2 88-92%**
  - **use minimum supplement necessary- may cause hypoventilation, especially in those who are chronic CO_2 retainers**
  - **Given via nasal cannula or mask**
- **Bronchodilators**
  - **Both beta agonists and anticholinergics effective**
  - **Albuterol ± ipratropium given via MDI/spacer or nebulizer q2-4 hrs as needed; Combivent Respimat ok if patient can inhale optimally**

Management of COPD Exacerbations, cont'd

- **Systemic corticosteroids**
  - **Reduces number of days to resolution and ↓ risk of treatment failure**
  - **Prednisone 40 mg/d (or equivalent) X5 days**
- **Antibacterial agents**
  - **Selected to cover *Haemophilus influenzae, Moraxella catarrhalis, and Steptococcus pneumoniae***
  - **Fever, increased amt of sputum, change in sputum color are indicators of possible bacterial component; avoid if sputum not purulent**
  - **Rx for ~5 days**

Management of COPD Exacerbations, cont'd

- **Theophylline *not recommended- GOLD 2019***
  - **May continue if using for maintenance Rx**
  - **Caution with altered $T_{½}$ due to liver congestion & with some antimicrobials**
- **Mechanical ventilation**
  - **Commonly required in exacerbations of severe COPD**
  - **Non-invasive methods using nasal or facial mask usually sufficient; otherwise need tracheal intubation**
  - **Difficult to wean severe COPD patients from mechanical support- need to obtain patient's input to plan for the "next" exacerbation**

Management of Acute Exacerbations of Asthma & COPD

	Asthma	***COPD***
Bronchodilators	Albuterol ± ipratropium	Albuterol ± ipratropium
Systemic steroids	Antiinflammatory doses 3-7 d or until PEF>70% prd.	Antiinflammatory doses ~5 days
Oxygen	To keep SpO_2 92-95%	To keep SpO_2 88-92%
Antibacterial Rx	No	~5 days if fever or Purulent sputum
2nd line Rx's	Heliox, $MgSO_4$	
Mechanical vent.	Uncommonly needed, but usu requires tracheal intubation	Common- noninvasive assist often ok