Asthma Part I

Pharmacotherapy I

Spring 2020

Dr. Abdallah Abukhalil

Abbreviations

CFCs: chlorofluorocarbons	DPI: dry-powder inhaler	FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity	ICS: inhaled corticosteroid	IgE: immunoglobulin E
LABA: long-acting β2-agonist	LTRA: leukotriene receptor antagonist	MDI: metered-dose inhaler
NAEPP: National Asthma Education and Prevention Program	PEF: peak expiratory flow	SABA: short-acting β2-agonist

GINA Definition

A heterogeneous disease, usually characterized by chronic airway inflammation.

It is defined by the history of respiratory symptoms such as **wheeze, SOB, chest tightness and cough that vary over time and intensity**, together with **variable** expiratory flow limitations.

EPR3 Simplified definition

Asthma is a common chronic disorder of the airways that involves a complex interaction of airflow obstruction, bronchial hyperresponsiveness and an underlying

inflammation. This interaction can be highly variable among patients and within patients over time

Chronic inflammatory lung disease

- reversible airflow obstruction
- increase in bronchial hyperresponsiveness (BHR)

Recurrent symptoms

- wheezing
- breathlessness
- chest tightness
- coughing especially at night or early morning

Impact of Asthma

~25.7 million people have asthma, including 7 million children

Each year, asthma is responsible for:

- 13 million missed school days
- 500,000 hospitalizations
- 10 million missed work days

Most common chronic disease in children in the United States.

Affects 9.5% of children 0-17 years old

Annual Costs: $19.7 billion

- Direct costs: $14.7 billion
- Rx medications: >$6 billion
- Indirect costs: $ 5 billion

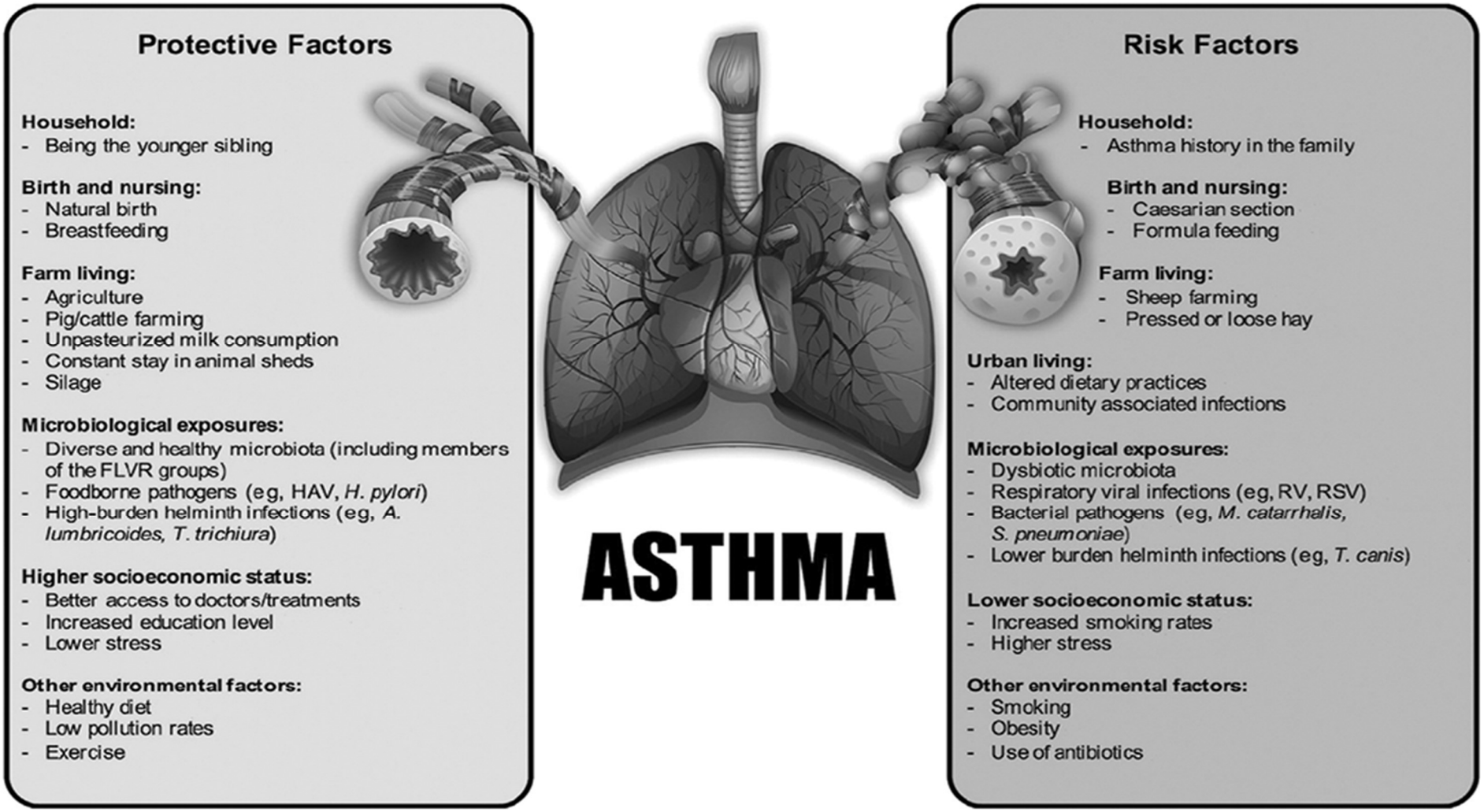
Etiology

Genetic factors account for 60-80% of susceptibility

- Complex genetic disorder

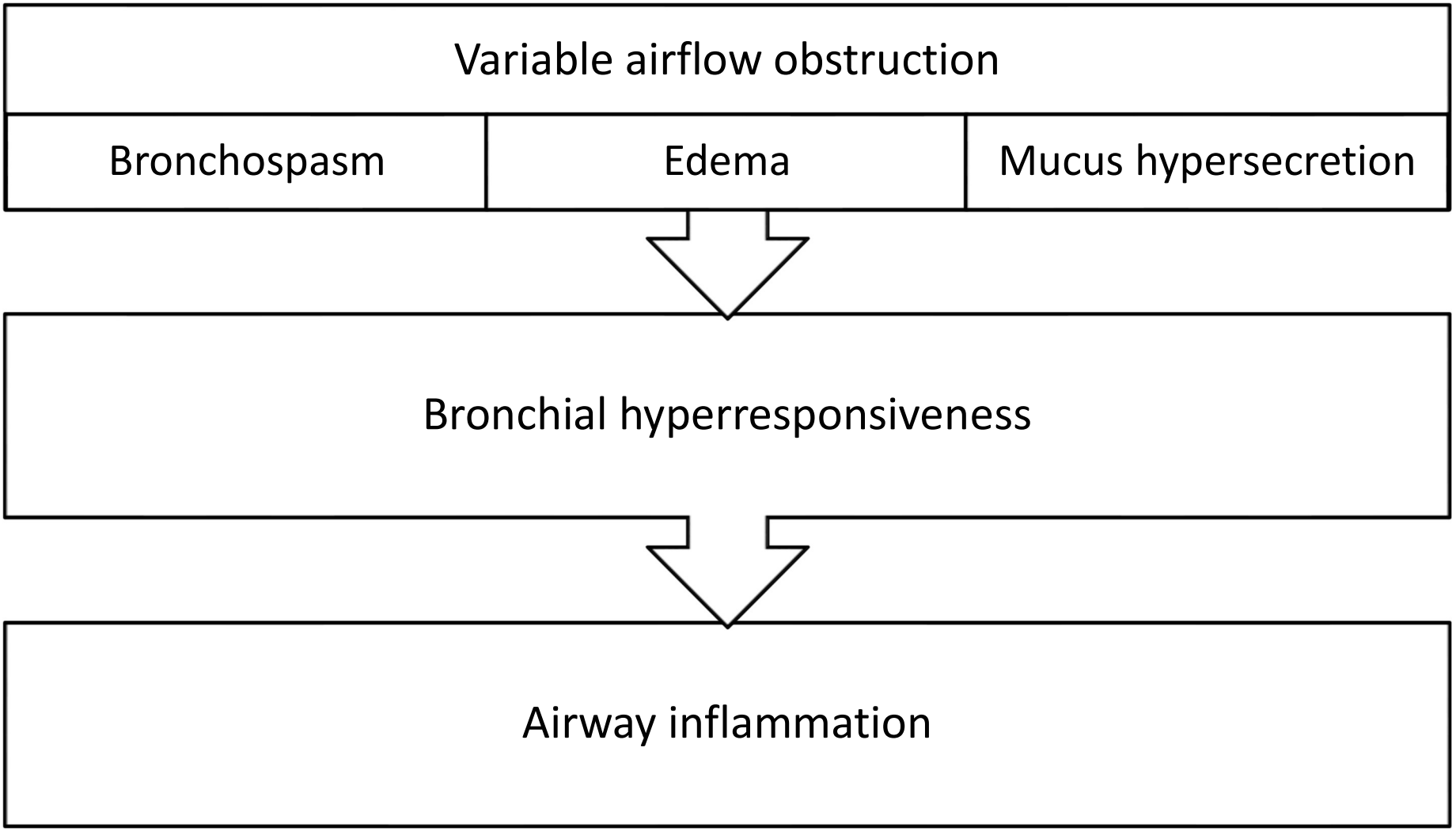
Environmental risk factors

- Allergen exposure
- Family size
- Exposure to second-hand tobacco smoke in infancy and in utero
- Socioeconomic status
- Respiratory syncytial virus infection
- Decreased exposure to common childhood infectious gents



Factors that are associated with protecting against, or risk for, developing asthma. These various factors have relative degrees of importance from patient to patient. FLVR, Faecalibacterium, Lachnospira, Veillonella, and Rothia spp; HAV, hepatitis A; RV, rhinovirus; RSV, respiratory syncytial virus. (Reprinted, with permission, from van Tilburg Bernardes E, Arrieta MC. Hygiene hypothesis in asthma development: Is hygiene to blame? Arch Med Res. 2017;48:717–726.)

Pathophysiology



Pathophysiology – Acute Inflammation

Activation of IgE (early phase reaction)

Mast cell and macrophage activation

Release of inflammatory mediators

- Histamine
- Eicosanoids
- Reactive oxygen species

Airway smooth muscle contraction, mucus secretion, vasodilation

Pathophysiology : Chronic Inflammation

Association between extent of inflammation and asthma severity

All airway cells involved become activated

- Epithelial cells
- Eosinophils
- Lymphocytes
- Mast cells
- Macrophages
- Neutrophils

Bronchial hyper-responsiveness to physical, chemical, pharmacologic stimuli

Airway remodeling

Marked hypertrophy and hyperplasia of bronchial smooth muscle

Mucous gland hypertrophy and excess mucus secretion

Pathophysiology – Airway Remodeling

Chronic inflammation leads to:

- Extracellular matrix fibrosis
- Increased smooth muscle →
- ↑ bronchial hyperresponsiveness
- Increased mucus gland mass/production
- Angiogenesis

Airway remodeling can lead to irreversible damage → COPD

Asthma Triggers

Allergens	Airborne pollens (grass, trees, weeds), house-dust mites, animal danders, cockroaches, fungal spores, mold
Environment	Cold air, fog, ozone, sulfur dioxide, nitrogen dioxide, tobacco smoke, wood smoke
Emotions	Anxiety, stress, laughter
Exercise	Particularly in cold, dry environments
Drugs / preservatives	Aspirin, NSAIDs (cyclooxygenase inhibitors), sulfites, benzalkonium chloride, nonselective β-blockers
Occupational stimuli	Bakers (flour dust); farmers (hay mold); spice and enzyme workers; printers (arabic gum); chemical workers (azo dyes, anthraquinone, ethylenediamine, toluene diisocyanates, polyvinyl chloride); plastics,

Asthma Triggers

Seasonal (grass, weeds, pollen, outdoor molds)

- Avoid doing yard work during peak season
- Wear a mask
- Wash hands/avoid touching face

Perennial (dust mites, pet dander, cockroaches)

- Wash bedding qweek in HOT water
- Impermeable covers
- Remove carpeting from bedrooms
- No pets in bedroom
- Humidty 30-50%

Diagnosis of Asthma

Episodic symptoms of airway obstruction

Airway obstruction is reversible

- FEV1 improves by 12% or more after SABAs

Peak Expiratory Flow Rate (PEFR)

- Based on age, gender and height

Alternative diagnoses excluded

- Asthma vs. COPD

Need:

PMH/PE/PFTs/additional tests

Clinical Presentation/Diagnosis Chronic Asthma

Wheezing	Dyspnea	Breathlessness	Chest tightness
Cough	Atopy	Severe acute asthma	Acute respiratory distress
Sx at night	Sx in early morning	Increased use of SABA	Sx with exercise

Diagnosis – Key Indicators

No single test can diagnose asthma!

- **Careful patient history**
- **Spirometry demonstrates reversible airway obstruction**

Spirometry (Lung Function Testing)

- **Reversibility following inhaled B2-agonist**
- **12% minimal improvement in FEV1 and > 200 ml improvement**
- **Normal spirometry results do not rule- out asthma**
- **Proper technique is essential to accurate results**
- **Variation in results is to be expected and support the diagnosis – higher variability with more severe disease**

Peek Expiratory Flow Rate (PEFR)

- **Based on age, gender and height**
- **For adults usual is about 300-600L/min**
- **Increase of >20% post inhaled B2-agonist**
- **For diagnosis: restricted to situations where spirometry is not readily available**
- **Should not be used in children <6 years**

Clinical Presentation/Diagnosis Chronic Asthma

Lung Function Testing

- Must confirm BOTH airflow limitation and variability in lung function

Airflow limitation (Spirometry)

- FEV1/FVC ratio decreased
- Adult normal: > 0.75-0.8
- Child normal: > 0.9

Variability in lung function

- Spirometry (bronchodilator reversibility test)
  - FEV1 (reduced in asthma):
  - Following SABA administration increases:
  - Adults: >12% and >200 mL from baseline
  - Children: >12% predicted

Peak Expiratory Flow

Testing twice daily x 2 weeks

- Adults: average >10% diurnal variability
- Children: average >13% diurnal variability

Child and adolescent female 6-20 years of age

Height (in)	42	46	50	54	57	60	64	68	72
Age: 6	134	164	193	223	245	268	297	327	357
8	153	182	212	242	264	287	316	346	376
10	171	201	231	261	283	305	335	365	395
12	190	220	250	280	302	324	354	384	414
14	209	239	269	298	321	343	373	403	432
16	228	258	288	318	340	362	392	421	451
18	247	277	306	336	358	381	411	440	470
20	266	295	325	355	377	400	429	459	489

Child and adolescent male 6-25 years of age

Height (in)	44	48	52	56	60	64	68	72	76
Age: 6	99	146	194	241	289	336	384	431	479
8	119	166	214	261	309	356	404	451	499
10	139	186	234	281	329	376	424	471	519
12	159	206	254	301	349	396	444	491	539
14	178	226	274	321	369	416	464	511	559
16	198	246	293	341	389	436	484	531	579
18	218	266	313	361	408	456	503	551	599
20	238	286	333	381	428	476	523	571	618
22	258	306	353	401	448	496	543	591	638
24	278	326	373	421	468	516	563	611	658
25	288	336	383	431	478	526	573	621	668

Asthma Diagnosis

YES

- Typically multiple symptoms
- Worse at night or early AM
- Varying in intensity and over time
- Triggers

NO

- Isolated cough with no other symptoms
- Chronic sputum production
- SOB with dizziness or paresthesia
- Chest pain
- Exercise induced dyspnea with noisy inspiration

Asthma Vs COPD

ASTHMA	COPD
• Nonproductive cough • Cough worse at night and early in the morning • FEV1 reversible • Lung damage can be reversible • Often related to allergies/triggers	• Productive cough • Cough worse throughout the day • FEV1 not reversible • Lung damage irreversible • Common history of smoking

Sample Questions for the diagnosis and initial assessment of asthma

A "yes" answer to any question suggests that an asthma diagnosis is likely. In the past 12 months.. . .

Have you had a sudden severe episode or recurrent episodes of coughing, wheezing (high-pitched whistling sounds when breathing out), chest tightness, or shortness of breath?

Have you had colds that "go to the chest" or take more than 10 days to get over?

Have you had coughing, wheezing, or shortness of breath during a particular season or time of the year?

Have you had coughing, wheezing, or shortness of breath in certain places or when exposed to certain things (e.g., animals, tobacco smoke, perfumes)?

Have you used any medications that help you breathe better? How often?

Are your symptoms relieved when the medications are used?

In the past 4 weeks, have you had coughing, wheezing, or shortness of breath.. .

At night that has awakened you?

Upon awakening?

After running, moderate exercise, or other physical activity?

Prognosis

If early childhood onset, half will no longer exhibit symptoms in later childhood

Mortality due to asthma is very low and usually related to suboptimal care

Long-term airway remodeling in some patients

structural changes resulting in narrowing of airway lumen

Risk Factors

More likely to develop fixed airflow limitation if:
Exposed to tobacco smoke
Exposed to noxious chemicals
Have occupational exposure
Have a low initial FEV1
Have chronic mucous hypersecretion
Have eosinophilia (blood or sputum)
Have poor control

Non-Pharmacological intervention

Avoidance of tobacco smoke exposure	• Provide advice and resources at every visit; advise against exposure of children to environmental tobacco smoke (house, car)
Physical activity	• Encouraged because of its general health benefits. Provide advice about exercise-induced bronchoconstriction
Occupational asthma	• Ask patients with adult-onset asthma about work history. Remove sensitizers as soon as possible. Refer for expert advice, if available
Avoid medications that may worsen asthma	• Always ask about asthma before prescribing NSAIDs or beta-blockers
Remediation of dampness or mold in homes	• Reduces asthma symptoms and medication use in adults

Non-Pharmacological intervention

Avoid Indoor air pollution	• Advise patients to use non-polluting heating and cooling sources.
Dealing with emotional stress	• Breathing techniques • Relaxation
Obesity	• Weight reduction if obese
(Allergen avoidance)	• (Not recommended as a general strategy for asthma)

Patient/Parent Education

- What is asthma?
- What defines well-controlled asthma?
- S/S of worsening asthma
- Role of different medications
- Medication administration technique
- Teach in simple language
- Teach/review/demonstrate
- Self management tools
  - written action plans
  - recognize early signs of deterioration
  - When and where to seek additional care
  - Control of triggers

Control of Comorbid Conditions

Treatment of these conditions may improve asthma control

- ASP (Allergic bronchopulmonary aspergillosis)
- GERD
- Obesity
- OSA (Obstructive sleep apnea)
- Rhinitis or sinusitis
- Stress or depression

Asthma Medication

Corticosteroids

- Inhaled
- Oral

Bronchodilators

- Short and long acting β2 agonists
- Short and long acting anticholinergics

Combination Inhalers

Antileukotriene agents

Mast cell stabilizers

Methylxanthines

Immunomodulators

Allergen immunotherapy

Comparative Pharmacology

Long-Term-Control Medications

- taken daily on a long-term basis to achieve and maintain control of persistent asthma
- Inhaled Corticosteroids/continuous OCS
- Long Acting Beta Agonists (LABA's)
- Long Acting Anticholinergics (LAMA's)
- Leukotriene modifiers (LTRA)
- Cromolyn & Nedocromil
- Methylxanthines: (Sustained-release theophylline

Quick-Relief Medications

- provide prompt relief of bronchoconstriction and its accompanying acute symptoms such as cough, chest tightness, and wheezing
- Short acting bronchodilators (SABA's)
- Systemic corticosteroids Burst
- Short acting Anticholinergics (SAMA's)
- GINA update also includes low-dose combination beclomethasone or budesonide with formoterol for both maintenance and rescue

Corticosteroids

Corticosteroids

Target main pathophysiologic problem

- improve lung function
- reduce impairment and risk associated with exacerbations
- only therapy shown to reduce risk of asthma death.
- Spirometry and PEF improvement takes 3-6 weeks.

Key Points: Safety of ICS's

- ICS's are the most effective long-term therapy available, are well tolerated & safe at recommended doses.
- The potential but small risk of adverse events from the use of ICS treatment is well balanced by their efficacy.
- Most benefit is achieved with relatively low doses, whereas the risk of adverse effects increases with dose.

Corticosteroids

Side Effects: Risk Factors

- Systemic side effects are rare
- Oral thrush and dysphonia (changes in voice).
- Rinsing the mouth with water after inhaling medication can reduce localized side effects.

More likely to have systemic side effects from medications if:

- Frequent OCS
- Long-term high-dose or potent ICS

More likely to have local side effects from medications if:

- High dose or potent ICS
- Poor inhaler technique

Efficacy

- Clearly demonstrate efficacy in reducing sx and risk of exacerbations by both nebulized and MDI administration
- The dose-response curve for ICS treatment begins to flatten at low to medium doses.
- Oral steroids acceptable for acute exacerbations or severe chronic disease
  - Prednisone burst

Patient Education: Inhaled Corticosteroid

Use every day regardless of how you feel

Not for use if you need relief now*

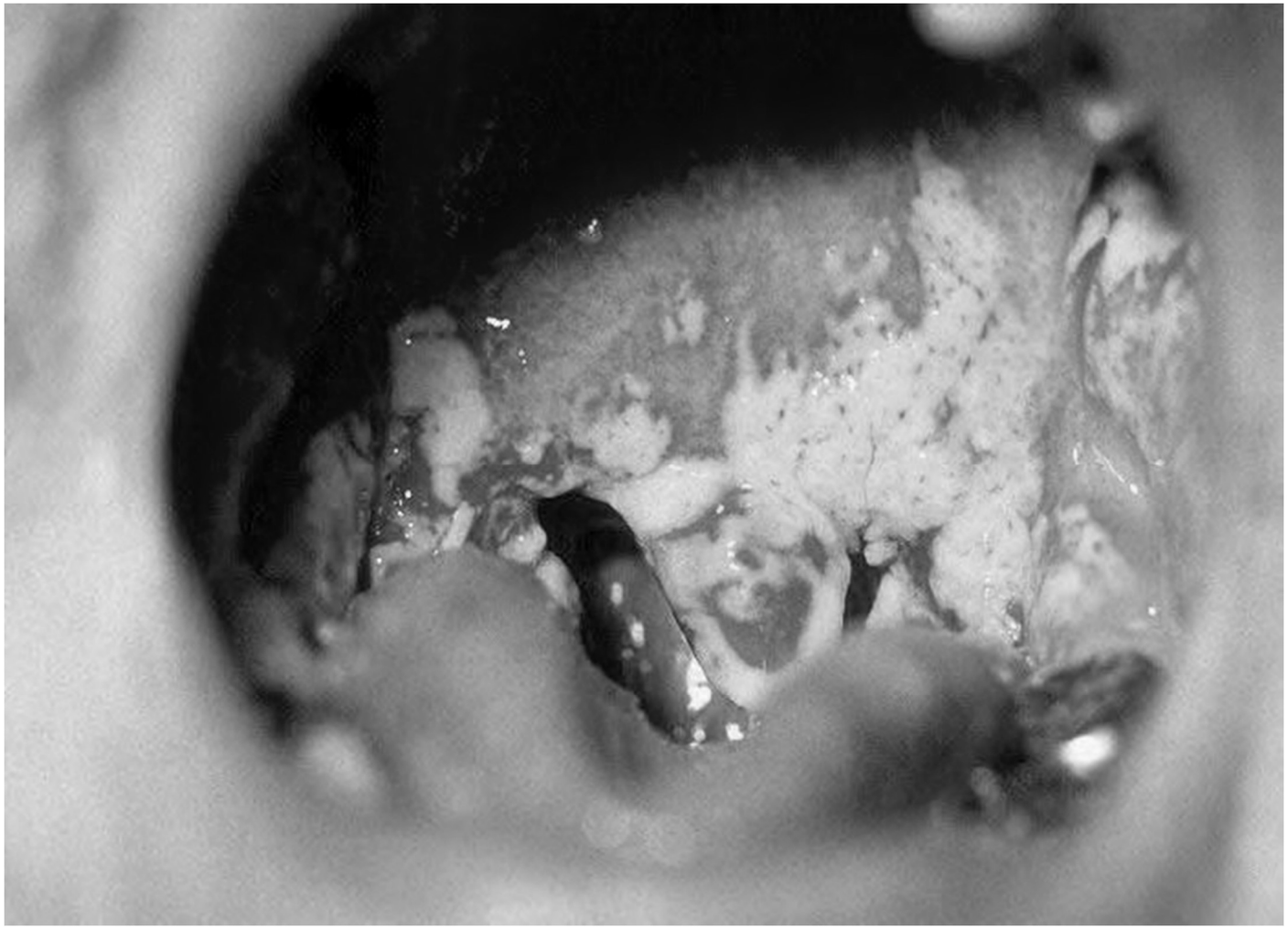
- GINA guidelines 2016 and later allow use of a specific ICS/LABA combination for maintenance and rescue

Appropriate use of inhaler and spacer device

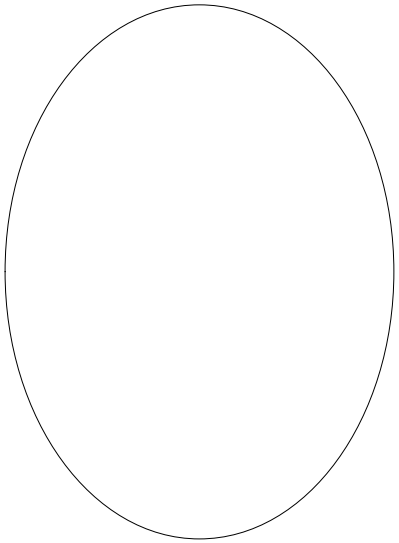
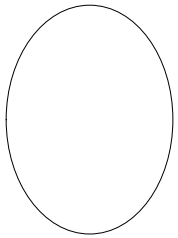
- Spacers or valved holding chambers (VHCs) used with non-breath-activated MDIs reduce local side effects.
- But there is no data on use of spacers with ultra fine particle hydrofluoroalkane (HFA) MDIs

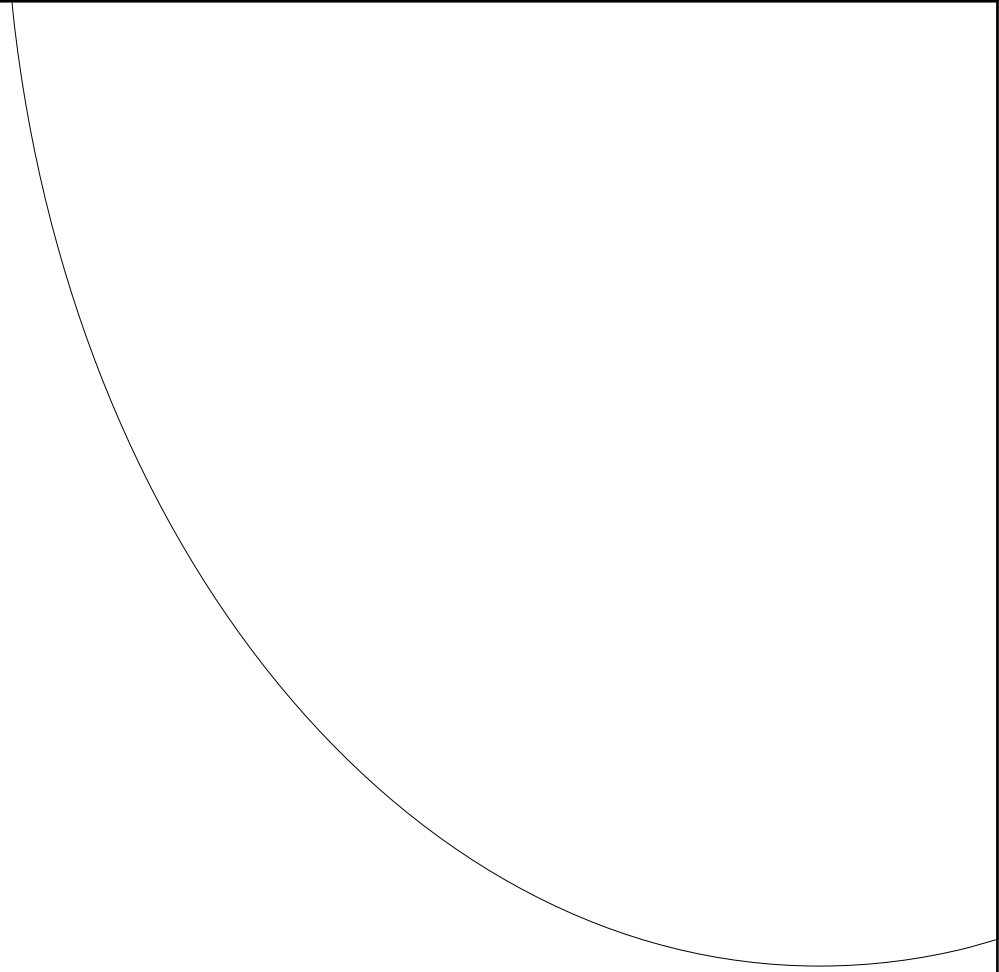
Rinse and spit

Oral Thrush



Generic	Brand	Dose	Adverse Effects	Comments
Corticosteroid Inhalers				
Beclomethasone MDI 40, 80mcg/puff	QVAR (HFA)	See ICS dosing table	Inhaled: oral candidiasis Hoarseness May slow bone growth in children but similar adult height Systemic: Cushing effects, slow growth, osteoporosis, hypertension, cataracts, glucose intolerance, skin thinning, myopathy, euphoria, depression, insomnia, Stomach upset, increased appetite	•1st line for persistent asthma •Holding chambers if needed for proper technique (only for MDIs); not needed or well studied with HFA inhalers, not for DPIs •Rinse mouth with water and spit after inhalation •Scheduled, not as needed* •Onset of symptom improvement is 5-7 days •Consider calcium and vitamin D supplementation in adults
Fluticasone MDI 44, 110, 220mcg/puff Fluticasone DPI 50, 100, 250mcg/puff	Flovent HFA Flovent Discus			
Mometasone DPI 110, 220mcg/puff	Asmanex Twisthaler			
Budesonide DPI 90, 180mcg/dose 0.25, 0.5, 1mg/2ml nebs	Pulmicort Flexhaler Respules			
Ciclesonide MDI 80, 160mcg/puff	Alvesco (HFA)			
Flunisolide MDI 80 mcg/puff	Aerospan (HFA)			



Anticholinergic

Anticholinergics

Ipratropium (Atrovent®), tiotropium (Spiriva®) aclidinium (Tudorza®)

- Prevent parasympathetic-mediated bronchoconstriction
- More effective and better tolerated than sympathomimetics

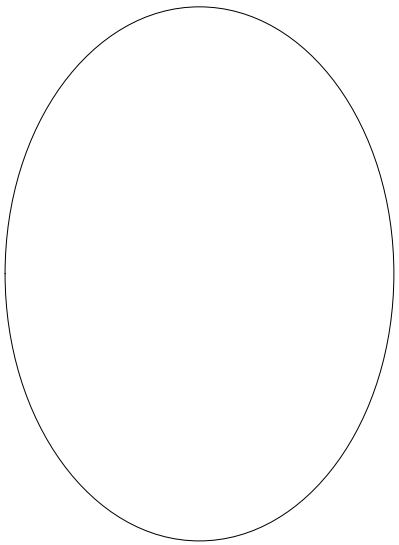
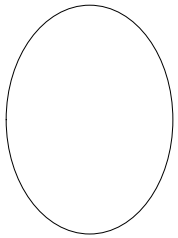
Tiotropium does not appear to slow decline in FEV1* but slightly reduces mortality**. Also shown to help as add-on to ICS + LABA for uncontrolled severe persistent asthma***

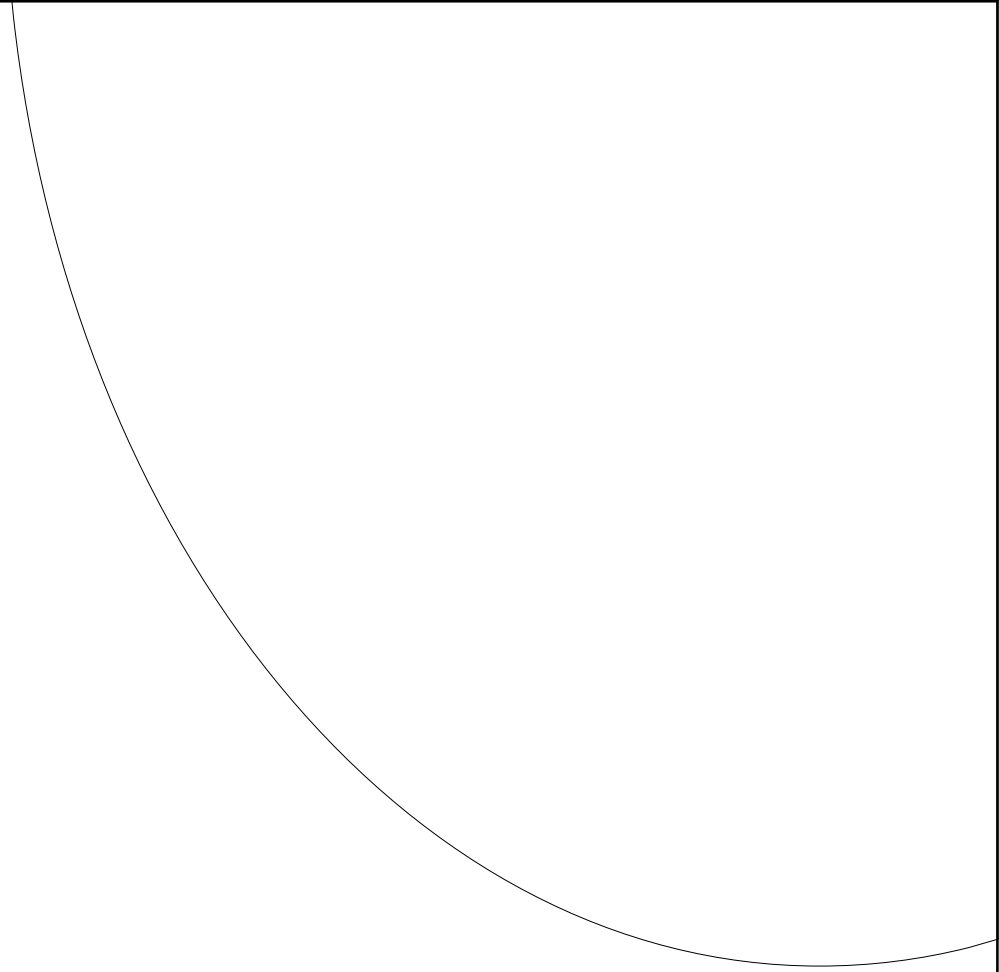
- GINA guidelines use tiotropium Respimat as a possible alternative or add-on in step 4 + 5 for adults (≥ 12 years) with a history of exacerbations

Ipratropium has slower onset of action than albuterol Useful if

- concomitant asthma/COPD
- intolerable adverse effects from b2-agonists
- refractory acute exacerbation
- Severe exacerbation

Generic	Brand	Dose	Adverse effects	Comments
Anticholinergics				
Ipratropium MDI 17mcg/puff	Atrovent HFA	2–4 puffs TID–QID (up to 12 puffs/24 hours)	Upper respiratory infection Bronchitis sinusitis Headache Flushed skin Blurred vision Tachycardia Palpitations Potential for increased cardiovascular risk	•Used mainly for COPD or for acute asthma exacerbations Duration: 2–8 hours •Also available for nebulization
Tiotropium DPI	Spiriva Respimat	2 puffs (1.25 mcg/puff) daily –Asthma 2 puffs (2.5 mcg/puff) daily – COPD		•Used mainly for COPD; Tio added to GINA in 2015 steps 4 and 5 for asthma •Long acting; not for rapid relief •Works best in neutrophilic asthma
	Spiriva HandiHaler	1 capsule (18 mcg) inhaled daily -- COPD		
Aclidinium DPI 400 mcg	Tudorza	Inhale BID		



Beta 2 agonist

Short and long acting B2 agonist

Stimulate B2 receptors

resulting in bronchodilation (Relax bronchial smooth muscle)

Inhibit subsequent bronchoconstriction response to stimuli

Adverse effects common with high doses

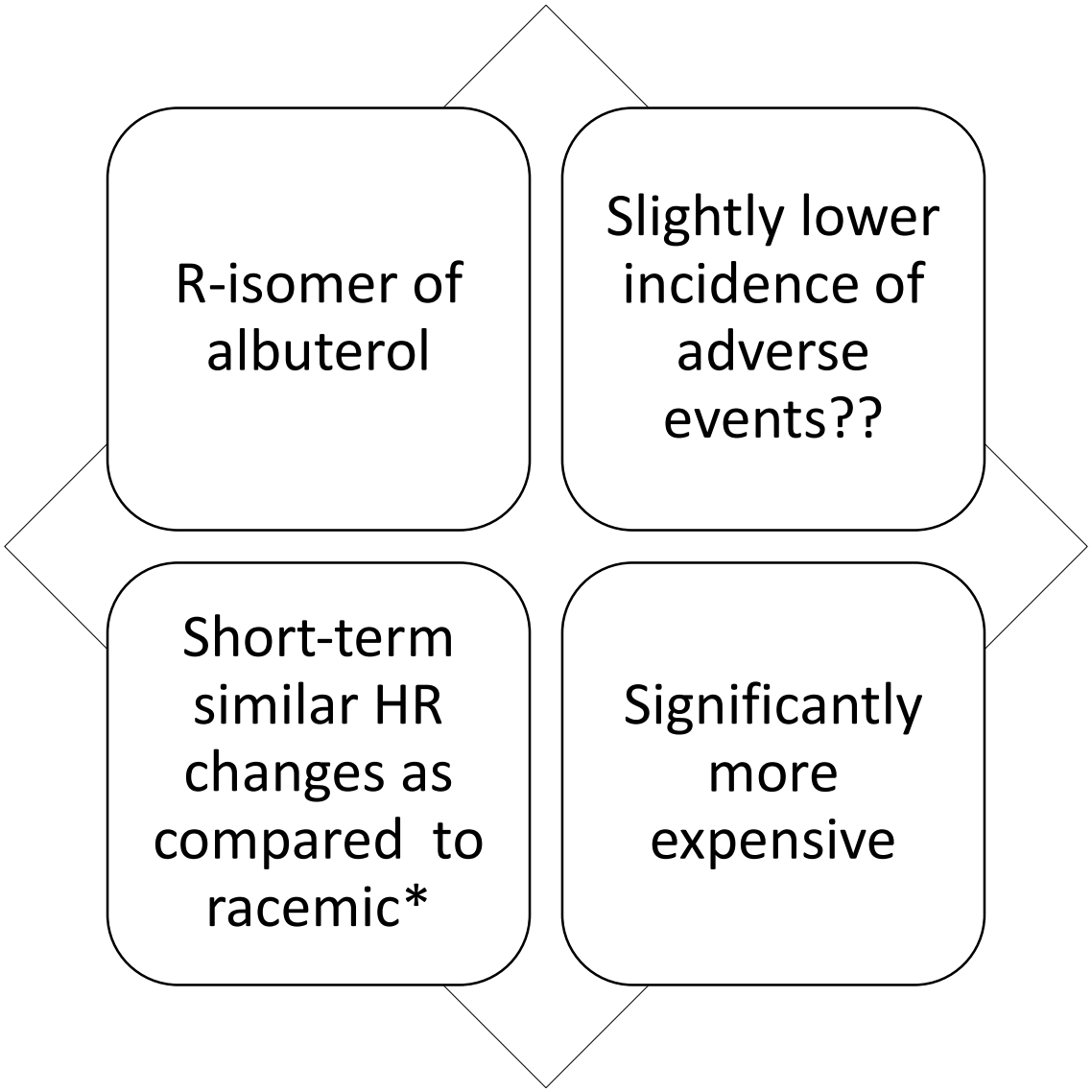
- Palpitations
- Chest Pain
- Tremor
- Tachycardia
- Nervousness

May provide symptomatic relief even if no objectively measured changes occur

Key Points and safety

- SABAs are the most effective medication for relieving acute bronchospasm
- Increasing use of SABA treatment or using SABA >2 days a week for symptom relief indicates inadequate control of asthma.
- Regularly scheduled, daily, chronic use of SABA is not recommended.

Xopenex “levalbuterol”



Key Points: Safety of SABA's

- SABAs are the most effective medication for relieving acute bronchospasm
- Increasing use of SABA treatment or using SABA >2 days a week for symptom relief indicates inadequate control of asthma.
- Regularly scheduled, daily, chronic use of SABA is not recommended.

SMART Study LABA Concerns

- SMART Study
- Salmeterol Multicenter Asthma Research Trial
- Patients randomized to salmeterol or placebo
- Study halted at 28 weeks
- 13/13,174 patients died in salmeterol group
- 3/13,179 patients died in placebo group
- risks higher in African-Americans than Caucasians
- Resulted in labeling changes and FDA public health advisory

LABA Safe Use Requirements

LABAs should be used for the shortest duration of time required

Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure compliance with both medications.

Adding a LABA to the tx of patients whose asthma is not well controlled on low- or medium-dose ICS can improve lung function, decrease symptoms, and reduce exacerbations and use of SABA for quick relief in most patients.

The FDA determined that a Black Box warning was warranted on all preparations containing a LABA.

LABA Safe Use Requirements

For patients who have asthma not sufficiently controlled with ICS alone, the option to increase the ICS dose should be given equal weight to the option of the addition of a LABA to ICS.

It is not currently recommended that LABA be used for treatment of acute symptoms or exacerbations.

Not for EIB (may mask poor control)

LABAs are not to be used as monotherapy for long- termasthma control.

Generic	Brand	Dose	Adverse effects	Comments
Short acting β_2 agonist (SABA)				
Albuterol MDI 90mcg/puff	Proventil HFA Ventolin HFA ProAir HFA ProAir RespiClick	2 puffs every 4–6 hours PRN	Tremor Tachycardia Palpitation Headache Hypokalemia Hypomagnesemia Hyperglycemia Muscular pain Tachyphylaxis	•Used for acute bronchospasm; regular use indicates poor control •Also available as solution for nebulization •Duration of effect (MDI): 3–4 hours (up to 6)
Levalbuterol MDI 45mcg/puff	Xopenex HFA	2 puffs every 4–6 hours PRN		•*R*-enantiomer of albuterol •Also available as a solution for nebulization •Duration (MDI): 3–4 hours (up to 6)
Pirbuterol 200mcg/puff	Maxair Autohaler	2 puffs every 4–6 hours PRN		•Breath-actuated MDI •Duration: 5 hours •Contained CFCs •Discontinued after 12/31/2013

Generic	Brand	Dose	Adverse Effects	Comments
Long acting β_2-Agonists (LABA)				
Salmeterol DPI 50mcg/puff	Serevent Diskus	Inhale 1 blister/ puff BID	Headache Tremor Tachycardia Electrolyte effects rare Muscular pain	•Not for acute symptoms •Should NOT be used as monotherapy for asthma •Duration: 8–12 hours
Formoterol DPI 12mcg capsule Formoterol 20mcg/2mL nebs	Foradil Aerolizer Perforomist	Inhale 1 capsule BID 20-mcg BID nebs		•Onset of action 1–3 minutes, but should not be used as acute therapy (unless combined with budesonide or beclometh) •Should NOT be used as monotherapy for asthma •Duration of MDI: 8–12 hours •Formoterol Aerolizer is indicated to prevent exercise-induced bronchospasm; use at least 15 min before exercise
Arformoterol 15mcg/2mL nebs	Brovana	15-mcg BID nebs		Arformoterol is the R,R-isomer of racemic formoterol
Indacaterol inhalation powder 75mcg capsule	Arcapta Neohaler	Inhale 1 capsule once daily		Indacaterol is only indicated for COPD NOT indicated for use in asthma at all Approved by FDA July 2011 Duration of action: 24 hours

Generic		Brand	Dose	Comments
Combination Inhalers				
Albuterol 103mcg/ puff plus Ipratropium 18mcg/puff MDI Albuterol 100mcg/puff plus Ipratropium 20mcg/puff		Combivent HFA Combivent Respimat	2 puffs QID 1 puff QID	•Primarily used for COPD •Combivent MDI contains CFC and is being phased out as of May 2013. • Combination solution for nebulization is also available as DuoNeb or generic

Generic		Brand	Dose	Comments
Combination Inhalers				
Fluticasone – salmeterol DPI 100/50, 250/50, 500/50 mcg/puff		Advair Diskus	1 puff BID	•Combination of ICS and LABA
Fluticasone – salmeterol MDI 45/21, 115/21, 230/21 mcg/puff		Advair HFA	2 puffs BID	
Budesonide – formoterol MDI 80/4.5, 160/4.5 mcg/puff		Symbicort (HFA)	2 puffs BID	
Mometasone – formoterol MDI 100/5, 200/5 mcg/puff		Dulera (HFA)	2 puffs BID	
Vilanterol/ Fluticasone Furoate		Breo Elipta (DPI)	Ihnaled once daily	FDA approved in combination For patients 18 years and older Once daily administration

Antileukotriens

Antileukotriene

Leukotriene receptor antagonists (LTRA)

montelukast (Singulair®), zafirlukast (Accolate®),

5-lipoxygenase inhibitor

zileuton (Zyflo®)

Blocks leukotriene pathway

(proinflammatory lipid mediators promote airway contraction)

Less effective than inhaled steroids but may be dose-sparing

Generic	Brand	Dose	Adverse Effects	Comments
Leukotriene modifiers (note: *FDA caution)				
Zafirlukast 10mg tablet 20mg tablet	Accolate	20 mg BID	Hepatotoxicity: Monitor LFTs (baseline, every month × 3 months, every 2–3 months for 1 year for montelukast and zafirlukast) Headache, GI upset *Risk of neuropsychiatric events (behavior and mood changes: aggression, agitation, anxiousness, dream abnormalities, hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior, tremor)	•Drug interactions: Warfarin, erythromycin, theophylline •For ≥ 5 years •Bioavailability decreases with food; take 1 hour before or 2 hours after meals
Montelukast Oral 10mg tablet Chewable 4 and 5mg Tablets Oral granules 4mg/ packet	Singulair	5–10 mg/day		•Drug interactions: Phenobarbital •FDA approved for use in ≥ 1 year; used in 6 months and older •Granules approved for 1 year and older •Chewable for 2-6 years Churg-Strauss syndrome associated with tapering doses of steroids
Zileuton 600mg CR tablet	Zyflo CR	1200 mg BID		•Drug interactions: Warfarin and theophylline •Only for those 12 years and older

Methylxanthins

Methylxanthines

Theophylline (Theo-Dur®), aminophylline

Stimulate bronchodilation through several mechanisms

Use declined due to risk for toxicity

- narrow therapeutic range
- frequent adverse effects

Can be steroid-sparing

Useful in nocturnal disease

Theophylline in the elderly

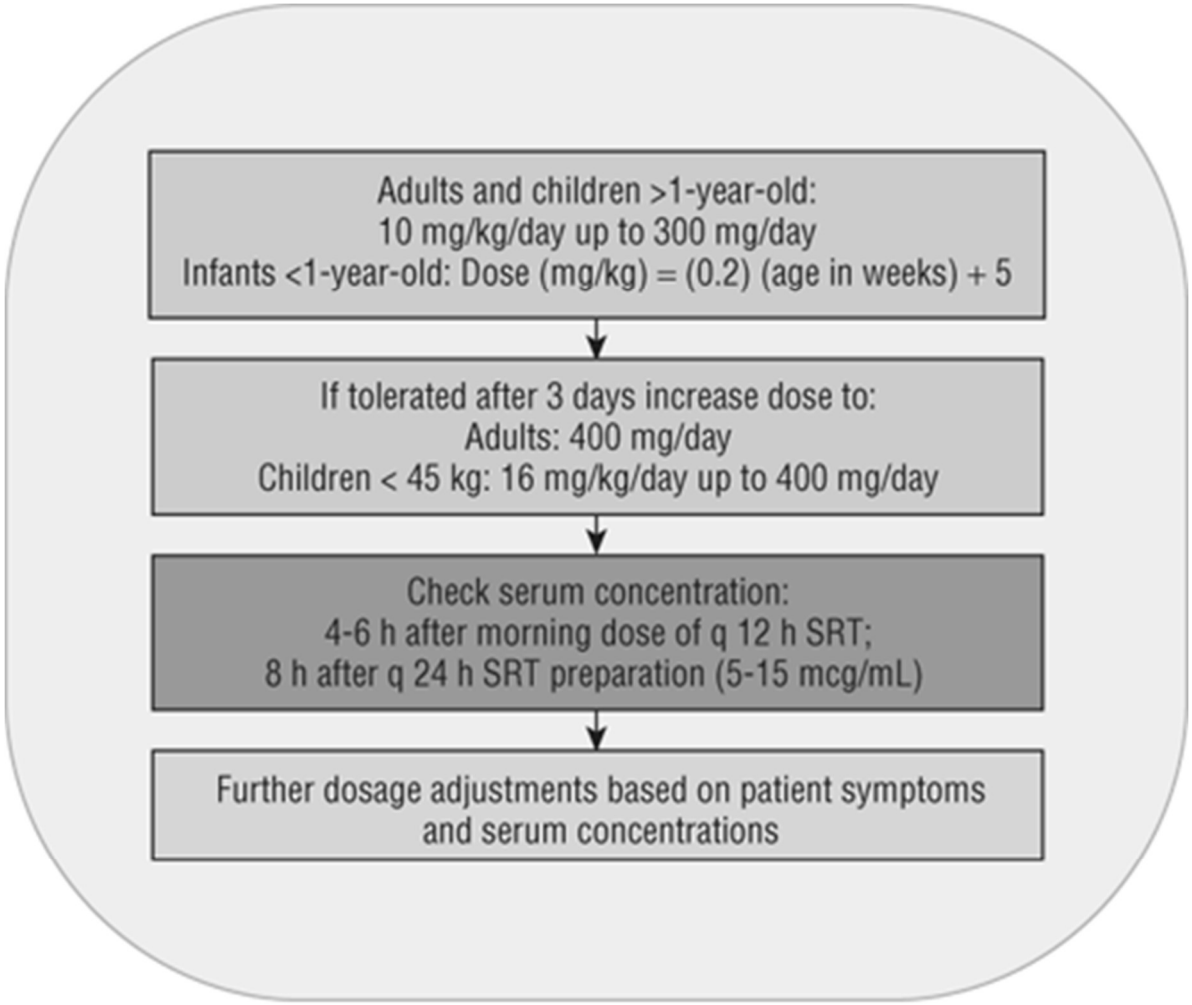
- Changes in clearance
- Increased clearance in elderly smokers
- Decreased clearance due to hepatic and renal problems
- Increased drug-disease interactions
- Increased drug-drug interactions
- On Beer's list as medication to be avoided.
- Stimulant

Decreased Clearance	% Decrease
Cimetidine	-25 to -60
Macrolides	-25 to -50
Allopurinol	-20
Propranolol	-30
Quinolones	-20 to -50
Interferon	-50
Thiabendazole	-65
Ticlopidine	-25
Zileuton	-35
Systemic viral illness	-10 to -50

Increased Clearance	% Increase
Rifampin	+53
Carbamazepine	+50
Phenobarbital	+34
Phenytoin	+70
Charcoal-broiled meal	+30
High-protein diet	+25
Smoking	+40
Sulfinpyrazone	+22
Moricizine	+50
Aminoglutethimide	+50

Clinically significant interactions occur with ≥ 20% inhibition or ≥ 50% induction

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: Pharmacotherapy: A Pathophysiologic Approach, 7th Edition: http://www.accesspharmacy.com/



Algorithm for slow titration of theophylline dosage and guide for final dosage adjustment based on serum theophylline concentration measurement. For infants younger than 1 year of age, the initial daily dosage can be calculated by the following regression equation: Dose (mg/kg) = (0.2) (age in weeks) + 5. Whenever side effects occur, dosage should be reduced to a previously tolerated lower dose.

Generic	Brand	Dose	Adverse Effects	Comments
Methylxanthine				
Theophylline Liquids, capsules, Sustained-release capsules (many dosage strengths)	Theo-Dur Uniphyl Theo-24	10 mg/kg/day (IBW) – Divided according to formulation - Adjust according to concentration Max: 16 mg/kg/ day (children < 12 years); 800 mg/day (adults) Smokers may need higher doses at more frequent intervals	At high levels: Nausea Vomiting CNS stimulation Headache Tachycardia, SVT Seizures Hematemesis Hyperglycemia Hypokalemia At usual levels: Insomnia GI upset Increased hyperactivity in some children Difficult urination in BPH	•Achieve concentrations of 5–15 mcg/mL •Beneficial for night symptoms •Not for acute relief •Duration: variable; up to 24 hours

Mast Cell Stabilizer

Mast cell Stabilizer

Cromolyn (Intal), nedocromil (Tilade)

Inhalers off the market

Only generic cromolyn nebulization solution available

Prevent mast cell degranulation

No bronchodilatory effect

Less effective than inhaled steroids

Virtually free from adverse effects

Immunomodulators

Immunomodulators

Meds loosely placed into same category because have documented effects on either humoral or cellular immune system

Omalizumab

Mepolizumab/Reslizumab

Methotrexate

Intravenous immunoglobulin G (IVIG)

Cyclosporine A

Macrolide antibiotics

- Useful for non-eosinophillic asthma*

Interleukin inhibitors:

- Anti-IL4: Dupilumab
- Anti-IL5: Benralizumab
- Anti-IL13: Lebrikizumab
- Anti-IL17: Brodalumab

CRTH2 Antagonists

- OC000459

KIT inhibitor

- Imatinib

Omalizumab "FYI"

Xolair®, approved 2003	Human/murine anti-IgE antibody	Administered as SQ injection q 2-4 weeks	Specific FDA approval
≥ 6 years old	Pts with IgE mediated allergic asthma	positive skin test or in vitro reactivity to a perennial aeroallergen	Moderate-severe persistent asthma not well controlled by ICS
Some anaphylactoid reactions	black-box warning added in 2007	Long-term safety unknown	Annual cost about $14,000

Mepolizumab “FYI”

Nucala approved 2015

- Interleukin-5 antagonist monoclonal antibody (IgG1 kappa)

Dose 100 mg SQ injection q 4 weeks

Specific FDA approval

- ≥ 12 years old
- Pts with eosinophilic phenotype
- Severe persistent asthma not well controlled by ICS (add on therapy)

Some hypersentivity reactions

- angioedema, bronchospasm, hypotension, urticaria, rash

Herpes zoster infections have occurred

Treat patients with pre-existing helminth infections before therapy

Annual cost about $32,000

Reslizumab

Cinqair approved 2015	Interleukin-5 antagonist monoclonal antibody (IgG4 kappa)	Dose 3 mg/Kg as IV infusion q 4 weeks over 20-50 mins
Specific FDA approval	≥ 18 years old	Pts with eosinophilic phenotype
Severe persistent asthma not well controlled by ICS (add on therapy)	Some anaphylactoid reactions -- Black Boxed warning	Malignancies were observed in clinical trials

Treat patients with pre-existing helminth infections before therapy	Annual cost about $12-31,000 (weight based)

Generic	Brand	Dose	Adverse Effects	Comments
Monoclonal antibody				
Omalizumab	Xolair	150-375mg SQ every 2–4 weeks Dose and frequency based on baseline IgE and weight in kilograms Do not inject > 150 mg per injection site	Urticaria Thrombocytopenia (transient) Anaphylaxis (rare) Malignancy Parasitic infections Lack of safety data beyond one year of therapy	•MOA: Inhibits IgE binding to high-affinity IgE receptors on mast cells and basophils •Indicated in moderate to severe persistent allergy- related asthma •Half-life: 26 days •Second-line therapy •Very expensive •Use in ≥ 12 years old •Administer in physician office to monitor for anaphylaxis (2hrs- 4 days) •Educate patients about risk of anaphylaxis, s/s and what to do if this happens •Has occurred with first dose and after many doses

Generic	Brand	Dose	Adverse Effects	Comments
Monoclonal antibody				
Mepolizumab	Nucala	100 mg SQ every 4 weeks	Common: Headache, inj site reaction, back pain, fatigue Rare: Hypersensitivy possible	•Interleukin-5 antagonist monoclonal antibody (IgG1 or 4 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older (mepolizumab) or 18 years and older (reslizumab), and with an eosinophilic phenotype Do not stop ICS or OCS suddenly during therapy. Decrease gradually if indicated. Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before therapy. If patients become infected and do not respond to anti-helminth treatment, discontinue until the parasitic infection resolves.
Reslizumab	Cinqair	3 mg/kg IV over 20-50 mins	Common: Oropharyngeal pain Rare: Muscle pain with increased CPK, Malignancy, Anaphylaxis	

Allergen Immunotherapy

Small doses allergens injected under the skin or given sublingually

- Over time, body may become less responsive to the allergens, causing less symptoms
- Allergy shots are given after careful skin testing for an allergy

During initial treatment, allergy shots are given once or twice a week

Higher dose monthly injections later

Adverse effects range from injection-site reactions to anaphylaxis

Magnesium

- Bronchodilating and anti-inflammatory effects during acute exacerbation
- Given as adjunct to standard therapy for
- severe exacerbation
- 2 Gm over 15 -30 minutes IV (adults)
- Consider 150 mg inhaled x 3 in 2 and older
- MOA for smooth muscle relaxation is unknown
- May potentiate beta2 agonists
- May antagonize Ca