Management of Asthma & COPD

The overall goals of of therapy consist of …

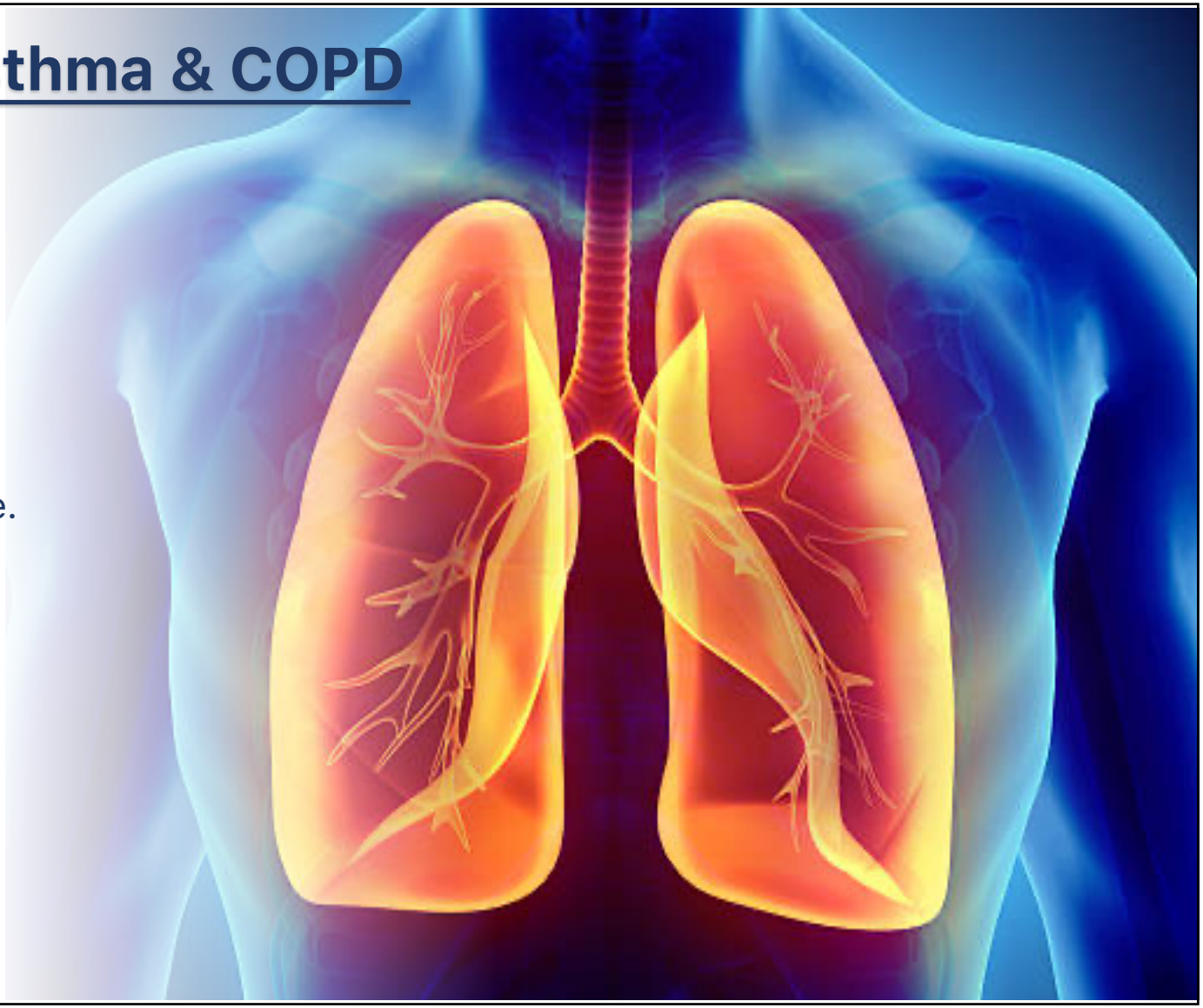
1. providing symptomatic control of asthma with normalization of lifestyle.

2. returning pulmonary function as close to normal as possible.

3. preventing chronic and troublesome symptoms (e.g., coughing, SOB).

4. preventing recurrent exacerbations.

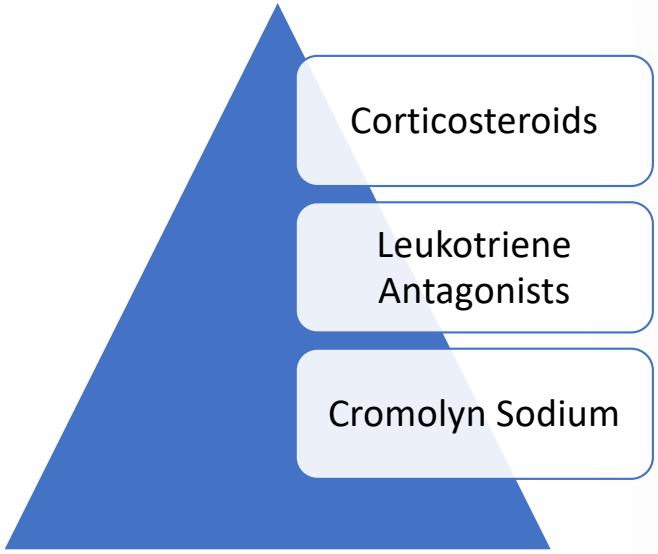
5. minimizing adverse effects from medications.

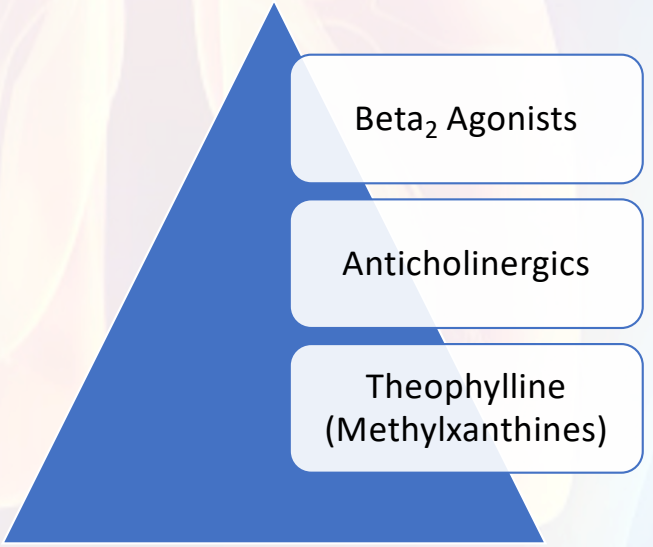


Management of Asthma & COPD

- The goal of pharmacologic therapy should not merely alleviate symptoms, but also prevent exacerbations and control chronic symptoms by reducing inflammation.
- Airway hyperresponsiveness is a major characteristic of asthma and may determine patient symptoms, disease severity, and possibly mortality
- Since airway inflammation is the underlying factor in airway responsiveness, drugs which target airway inflammation are considered first-line agents.

Bronchial Inflammation → Airway Hyperresponsiveness → Airflow Obstruction → Asthma





Management of Asthma & COPD

PATHOGENESIS

Genetic Factors ←→ Environmental Factors

- Air Pollution
- Allergens
- Cigarette Smoking
- Viral Infectious Agents

Bronchial Smooth Muscle Contraction

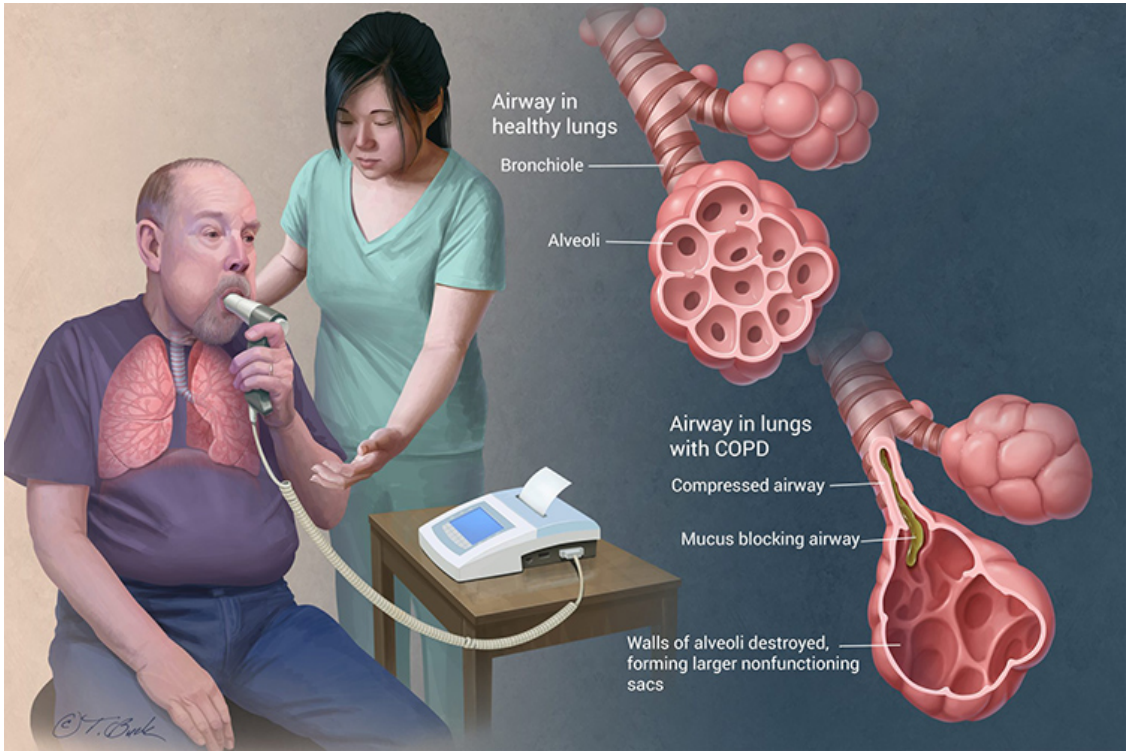
MANAGEMENT

Nonpharmacologic Therapy

- Patient Education
- Environmental Control
- Immunotherapy
  - Vaccinations
    - Influenza (Flu) Shot
    - Covid-19 Shot
    - RSV Shot
      (Resp Syncytial Virus)
    - Pneumococcal Shot
      (Pneumovax, Prevnar)

Pathogenesis of COPD

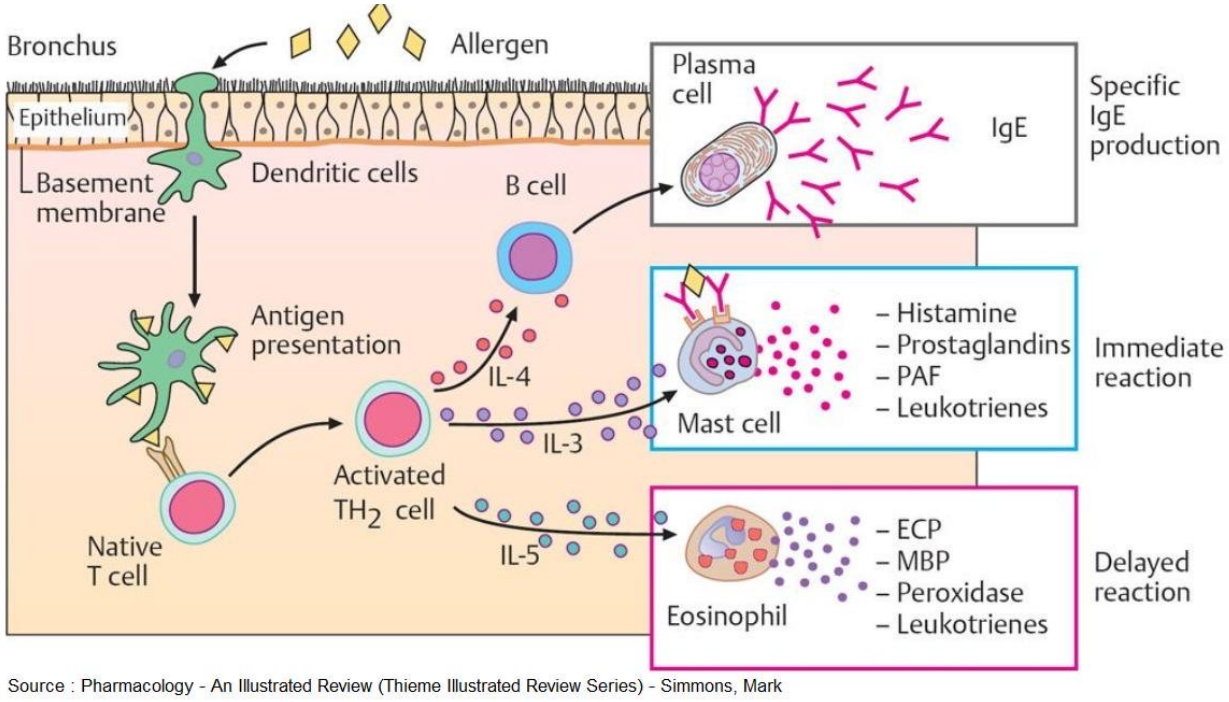
- COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms due to airway obstruction and alveolar abnormalities usually caused by significant exposure to noxious particles or gases (e.g., tobacco)
- The chronic airflow limitation that characterizes COPD is caused by small airway disease (bronchiolitis) and destruction of lung parenchyma (emphysema).
- Chronic inflammation causes irreversible structural changes in COPD, characterized by small airway narrowing, mucociliary dysfunction, and destruction of lung parenchyma.



Pathogenesis of Asthma

- Allergens attach to and are taken up by dendritic cells in the ciliated respiratory epithelium.
- Antigen is presented to native T-cells, which differentiate into activated T-helper (TH_2) cells.
- TH_2 cells release cytokines:
  - IL-4 activates B cells → B cells differentiate into plasma cells
    → plasma cells release IgE
    → IgE attach to mast cells
    → mast cells degranulate when allergen binds to two IgE molecules
  - IL-3 activate mast cells

    → mast cells release inflammatory mediators: histamine, PG, and LT → cause bronchoconstriction, bronchospasm, mucosal swelling, and mucus production.

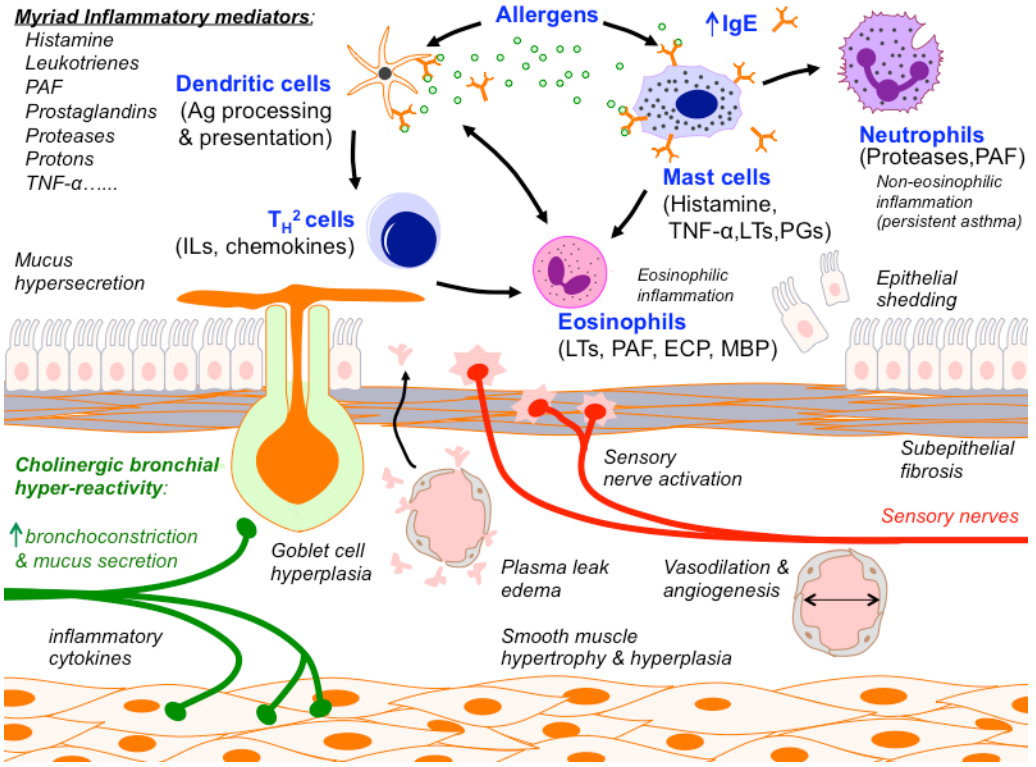


Source : Pharmacology - An Illustrated Review (Thieme Illustrated Review Series) - Simmons, Mark

ECP: Eosinophil Cationic Protein; MBP: Major Basic Proteins; PAF: Platelet Activation Factor

Progressive Structural Changes in Severe Asthma

- In severe asthma, many inflammatory cells are recruited and activated to release different cytokines and inflammatory mediators that cause bronchoconstriction, vasodilation, edema, mucus hypersecretion, and activation of sensory nerves.
- In time, structural changes develop in the airways: epithelial shedding, thickening of the basement membrane, subepithelial fibrosis, blood vessel proliferation (angiogenesis) and blood vessel dilation, hyperplasia of mucus-secreting cells (hypersecretion of mucus), smooth muscle hypertrophy and hyperplasia.
- In the late phase of allergen response, recruitment of multiple subtypes of immune cells (eosinophils, neutrophils, and memory T-cells) release multiple inflammatory mediators that cause cholinergic hyperactivity → increase mucus secretion and bronchoconstriction in severe asthma that require inhaled anticholinergic agents.



ECP: eosinophil cationic protein; LT: leukotrienes; MBP: major basic protein; PAF: platelet activating factor; PG: prostaglandins

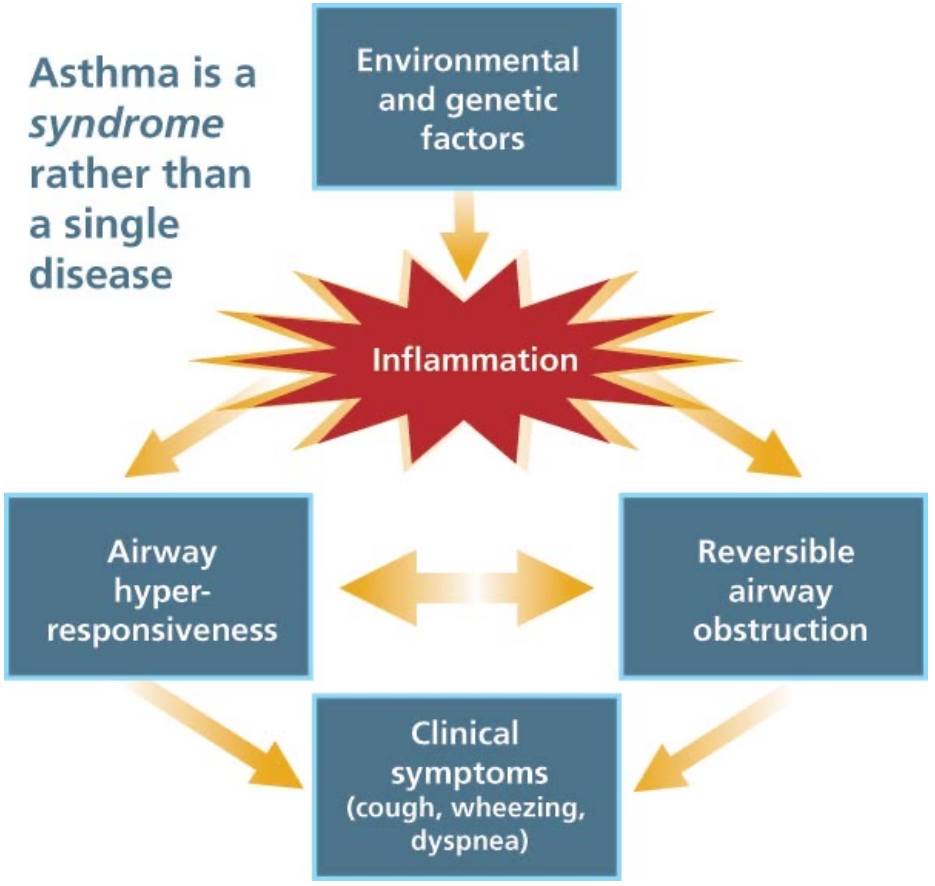
Therapeutic Options in Asthma

Anti-Inflammatory Agents

- Corticosteroids (Inhaled, Oral, Injectable)
- Mast Cell Stabilizer (Inhaled)
  - Cromolyn Sodium (Intal)
- Leukotriene Antagonists (Oral)
  - Montelukast (Singulair)
- Immunomodulators (Injectable)
  - Omalizumab (Xolair)

Bronchodilators

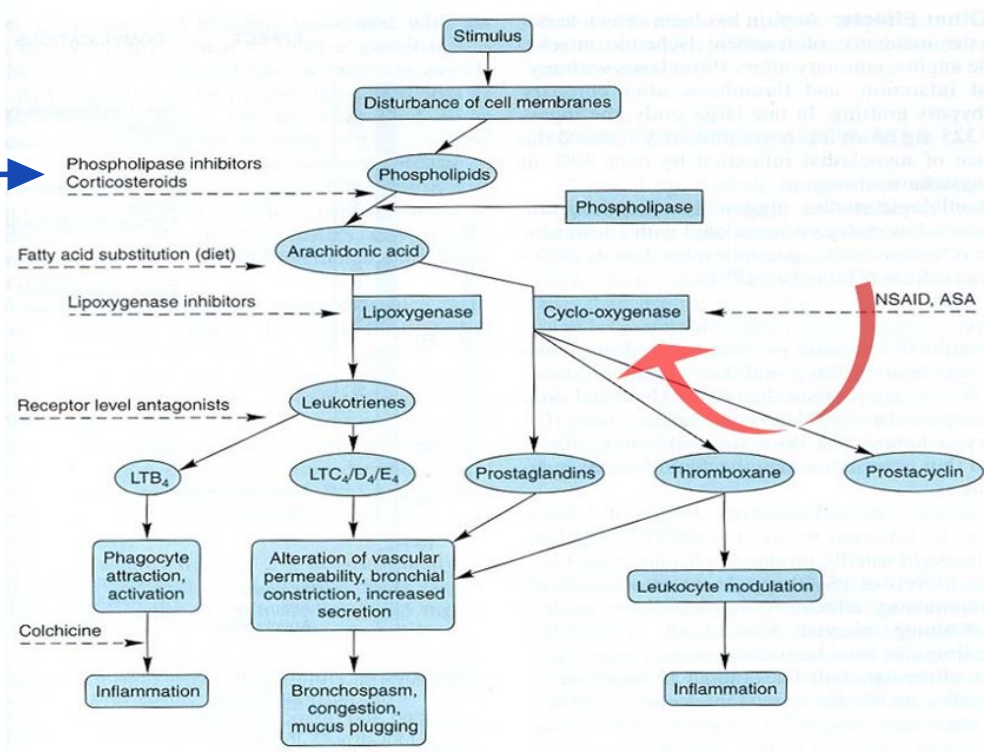
- Beta-2 Agonists (Inhaled, Oral, Injectable)
  - Albuterol (Proventil, Ventolin)
- Anticholinergic Agents (Inhaled)
  - Ipratropium Bromide (Atrovent)
- Methylxanthines (Oral, Injectable)
  - Theophylline (Theo-Dur)



Inhaled Corticosteroids (ICS)

Beclomethasone (QVAR), Budesonide (Pulmocort), Fluticasone (Flovent), Triamcinolone (Azmacort), Mometasone (Asmanex), and Flunisolide (AeroBID)

- Mechanisms of Action: ICS are nonspecific suppressors of inflammation
  - ICS inhibit arachidonic acid metabolism, resulting in the decreased production of leukotrienes and prostaglandins
  - ICS reduce the migration and activation of inflammatory cells by inhibiting cytokine production
  - ICS increase the responsiveness of the beta$_2$-receptors of airway smooth muscle



Inhaled Corticosteroids (ICS)

- Side Effects: cough, dysphonia, oral thrush (candidiasis)
  - cough, due to the additive oleic acid, may occur with the use of some corticosteroid inhaler products; but is minimized by the use of spacers
  - reversible dysphonia may occur with deposition of the steroid on vocal cords
  - localized infection with *Candida albicans* may occur in the mouth, pharynx, or the larynx

- Major Adverse Effects of Systemic Corticosteroids

Metabolic & Endocrine Hyperglycemia Adrenal Insufficiency (i.e., HPA-Axis Suppression) Immune System Immunosuppression (risk of infection) Hematologic Leukocytosis Cardiovascular Fluid Retention Hypertension	Neuropsychiatric Dysphoria/Depression Mania/Psychosis Euphoria Insomnia Ophthalmologic Elevated Intraocular Pressure Cataract Formation Exophthalmos Gastrointestinal Gastritis Peptic Ulcer Disease (PUD)	Bone & Muscle Osteoporosis Myopathy Dermatologic & Appearance Cushingoid Appearance Facial Erythema Skin thinning Weight Gain Hirsutism Acne Striae

Inhaled Corticosteroids (ICS)

- Prevention of Oral Thrush
  - the incidence of oral thrush may be reduced by the use of a spacer and with rinsing the mouth (swish and spit) following use of an ICS
- Treatment of Oral Thrush
  - Nystatin (Mycostatin) Oral Suspension: swish and swallow 5 ml (1 tsp) QID
  - Clotrimazole Troches (Mycelex): 1 troche five times daily for 7-14 days

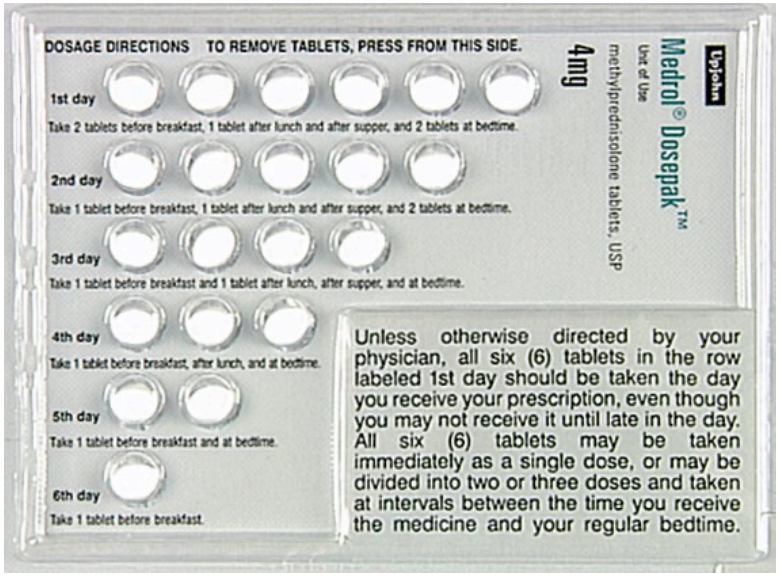
Cromolyn (Intal) & Nedocromil (Tilade) Inhalers

- Cromolyn and nedocromil are non-steroidal, but less potent anti-inflammatory agents
- Mechanism of Action: Cromolyn and nedocromil stabilize the mast cell membrane
  → prevents degranulation of mast cells
  → inhibits release of inflammatory mediators (i.e., histamine, leukotrienes, prostaglandins)
- Side Effects: Cough and throat irritation
  - Cromolyn and nedocromil are generally well tolerated have favorable side effect profiles and may be considered for use in patients with mild asthma
- Concomitant therapy with cromolyn or nedocromil with inhaled corticosteroids may permit reduction in the dose of ICS in patients requiring high doses of the latter

First Generation

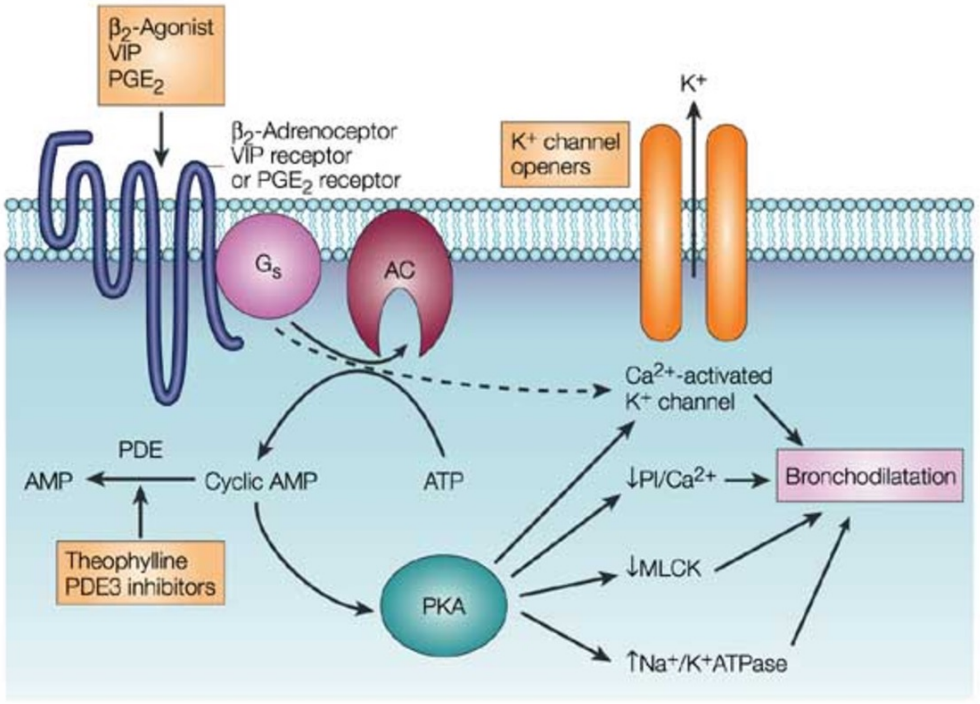
Oral Corticosteroid Therapy

- Oral corticosteroid therapy can be divided into 2 approaches: (1) “burst” tx and (2) long-term tx
  - Burst Regimens of 7-14 days are appropriate for acute exacerbations of asthma
    - HPA-axis Suppression: Little or no residual effect on the HPA-axis occurs after burst therapy and tapering is not necessary to prevent adrenal insufficiency; however, it is often useful to taper the corticosteroid dose to evaluate the effect of withdrawal on a patient’s asthma symptoms
    - Example of Burst Regimen: Prednisone each morning: 60 mg on days 1-3; 50 mg on day4; 40 mg on day 5: 30 mg on day 6; 20 mg on day 7; 10 mg on day 8; 5 mg on day 9-10; then stop. Dispose: Prednisone 10 mg # 35 tablets
    - Medrol Dosepak (methylprednisolone 4 mg tabs) is a convenient and easy-to-use oral corticosteroid taper
  - Side Effects of Long-Term Tx of Systemic Corticosteroids: HPA-axis suppression, weight gain, hypertension, hyperglycemia, osteoporosis, myopathy, psychiatric disturbance, and cataracts

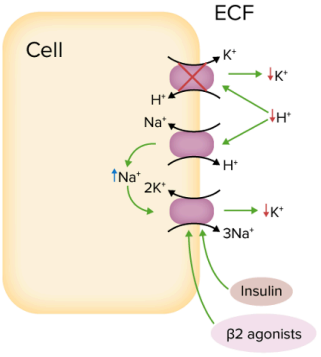


Inhaled Beta-2 Agonists

- Mechanism of Action:
  Beta-2 agonists stimulate adenylyl cyclase (AC)
  → converts ATP to cAMP
  → stimulates protein kinase A
  → bronchodilation
- Side Effects: tachycardia, tremors, anxiety, hypokalemia
  Note: all "selective" beta-2 agonists will exert beta-1 agonist effects when used in higher doses



- Albuterol 10-15 mg HHN is indicated for treatment of hyperkalemia
  → beta-2 stimulation (skeletal muscle) → increases cAMP
  → stimulates $Na^+/K+$ pump
  → actively transports and shifts K+ intracellular
  → decreases serum K^+



Inhaled Beta-2 Agonists

- Comparison of Selected B-Agonist Bronchodilators

	Agent	Dosages Forms[a]	Receptor Selectivity β_1	Receptor Selectivity β_2	β_2 Potency[b]	Duration of Action (hr)[c]
First Generation	Epinephrine[d]	Inj, AS, MDI	+++	+++	2	0.5–2
	Isoproterenol (Isuprel)	Inj, AS, MDI, SL	++++	++++	1	0.5–2
	Isoetharine (Bronkosol)	AS, MDI	++	+++	6	0.5–2
	Metaproterenol (Alupent)	AS, MDI, PO	++	++	10	3–4
	Terbutaline (Brethine)	Inj, MDI, PO, AS	+	++++	4	4–8
Second Generation	Albuterol (Ventolin, Proventil)	AS, MDI, PO	+	++++	2	4–8
	Bitolterol (Tornalate)	MDI	+	++++	4	4–8
	Pirbuterol (Maxair)	MDI	+	++++	4	4–8
Third Generation	Formoterol	MDI	+	++++	0.24	8–12
	Salmeterol (Serevent)	MDI	+	++++	0.50	12

Inhaled Beta-2 Agonists

- Long-Acting Beta-2 Agonists (LABA): Salmeterol (Serevent) & Formoterol (Performomist)
  - Compared to SABA, salmeterol (but not formoterol) has slower onset of action (15-30 mins)
  - LABA provide long-term prevention of symptoms, usually added to ICS in combination products: Symbicort MDI (Budesonide + Formoterol) and Advair MDI (Salmeterol + Fluticasone)
  - Advantages of LABA: (1) BID administration is effective in preventing nocturnal asthma symptoms, and (2) LABA taken in the morning provides 12-hour prophylaxis in children attending school.

Inhaled Beta-2 Agonists

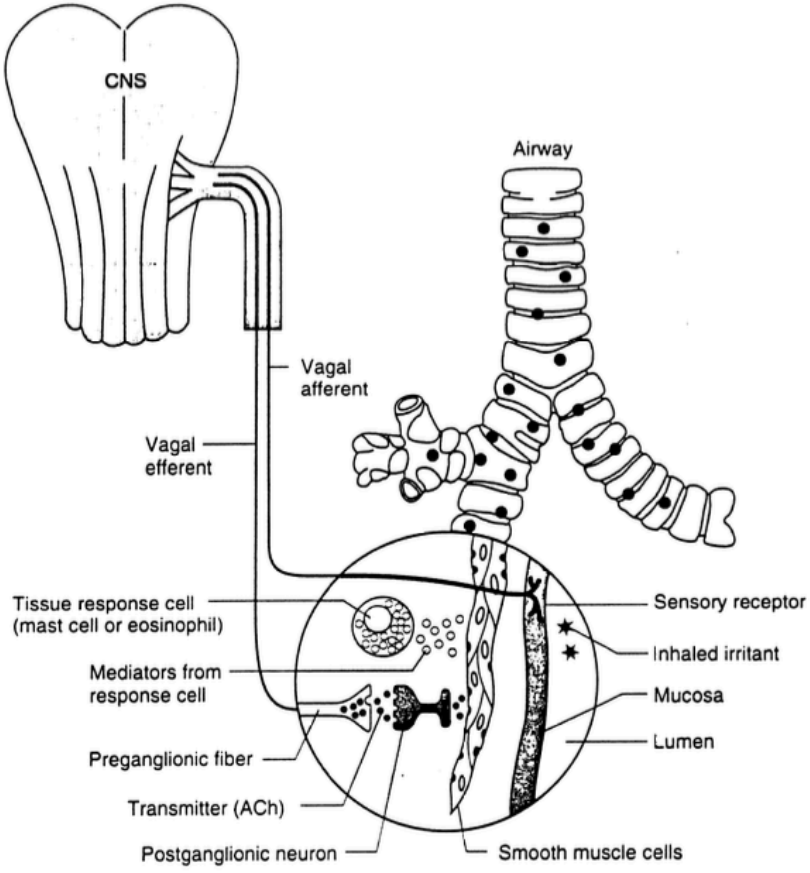
- Levalbuterol (Xopenex)
  - Levalbuterol at ~~hone~~ half the mcg dose produces clinically comparable bronchodilation as albuterol → reduces cardiac adverse effects (tachycardia) and is preferred in patients with atrial fibrillation.

	BETA-1	BETA-2
ALBUTEROL	+	++++
LEVALBUTEROL (Xopenex)	+ / -	+++

Inhaled Anti-Cholinergic (Anti-Muscarinic) Agents (SAMA & LAMA)

SAMA: Ipratropium Bromide (Atrovent)
LAMA: Tiotropium Bromide (Spiriva)

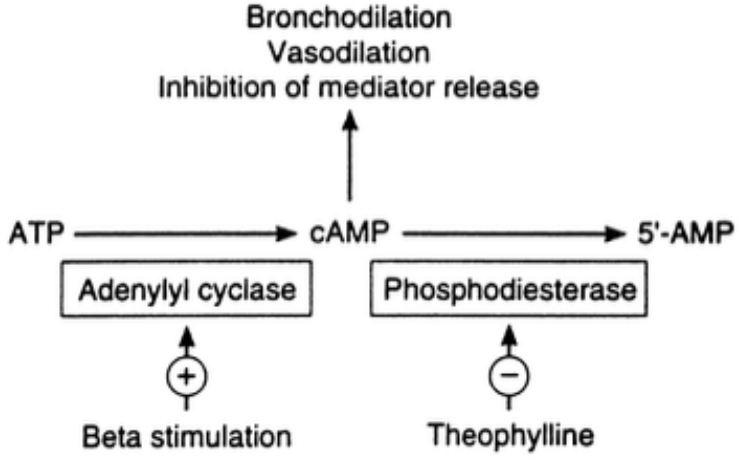
- MOA: (1) inhibit muscarinic cholinergic receptors → bronchodilation, and (2) reduce intrinsic vagal tone of the airways → block reflex bronchoconstriction secondary to irritants or to GERD
- These agents are more effective in COPD, in which vagal-mediated bronchoconstriction is predominant, than in asthma
- Since SAMA and LAMA are less effective than beta-2 agonists in treatment of asthma/COPD, they are usually combined with beta-2 agonists: DuoNeb (albuterol 2.5 mg / ipratropium 0.5 mg in 3 ml saline)
- Side Effects: systemic anticholinergic effects include dry mouth, blurred vision, urinary retention, etc…



Methylxanthine: Theophylline (Theo-Dur)

- General Considerations
  - Theophylline is not effective as an aerosolized inhaler and must be given orally or intravenously → increases systemic side effects.
  - Theophylline is less effective as a bronchodilator than beta-2 inhaled agonists.
  - Theophylline causes many drug-drug interactions and serious adverse effects.
  - Theophylline has a narrow therapeutic range (10-20 mcg/ml) → potentiates toxicities.
  - Theophylline is considered a 3rd or 4th line adjunctive agent in persistent asthma.

- Mechanisms of Action: Besides smooth muscle relaxation, the beneficial effects of theophylline that have been postulated have included an anti-inflammatory effect, an improvement in mucociliary clearance, increased diaphragmatic contractility, and increased respiratory drive.
- Side Effects & Toxicities: nausea, vomiting, dyspepsia, GI reflux, diarrhea, tachycardia, insomnia, headaches, irritability, arrhythmias, seizures, cardiac arrest, death.



Acute Exacerbations of Asthma

- The first indication of an exacerbation is either an increase in symptoms or a decline in the PEFR below the patient's normal range. (PEFR: peak expiratory flow rate, which correlates with FEV_1)
- The "Zone System" uses the PEFR to provide an objective measurement of exacerbation severity
- Many moderate-severe exacerbations are best treated at home with a short course ("burst tx") with oral prednisone.
- The failure of symptoms and the PEFR to improve 6 hour after oral corticosteroids are taken indicates an inadequate response and consideration should be given to an ER evaluation.
- Dr. Roger Bone: Patients should have oral prednisone on hand so that they can take 40-60 mg as soon as they begin to have an acute attack, since oral or intravenous corticosteroids take about 6 hours before they significantly improve PEFR
  - The challenge is to educate patients to begin taking oral prednisone when symptoms dictate.
  - The patient's job is to take the prednisone and the clinician's job is to taper the dosage.

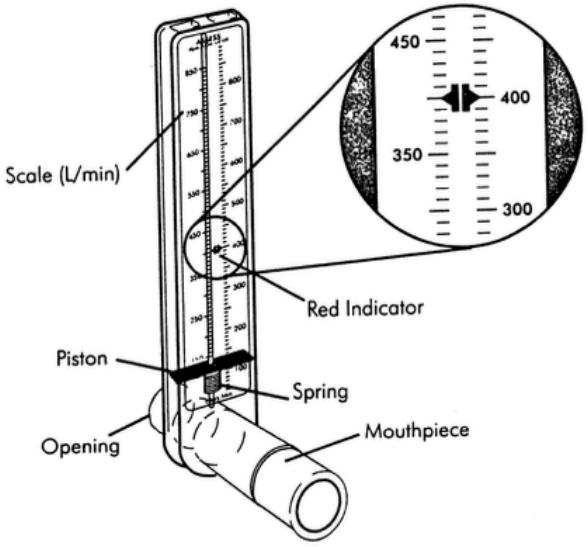


Fig 19.5 Peak Flow Meter

TABLE 5.—*Zone System of Peak Expiratory Flow (PEF) Monitoring*

Zone	*Interpretation*	*Best PEF Rate, %*	*AM/PM PEF Variability, %*
Green	All clear	>80	<20
Yellow	Caution	50-80	20-30
Red	Alert	<50	>30

Complicating Factors

- Gastroesophageal Reflux Disease (GERD)
  - GERD may trigger severe bronchospasm and increase airway hyper-responsiveness
  - The reflux of acidic fluid into the upper esophagus or with aspiration into the trachea is a common cause of refractory asthma.
  - Treatment: (1) Proton-Pump Inhibitors: Omeprazole (Prilosec), Pantoprazole (Protonix) and/or (2) Prokinetic Agent / Antiemetic: Metoclopramide (Reglan)

- Rhinitis / Sinusitis
  - Rhinitis and sinusitis may also make asthma difficult to control.
  - Recurrent postnasal drip irritates the larynx and trachea and increases airway hyperresponsiveness → bronchospasm.
  - Treatment: (1) Antihistamines: Cetirizine (Zyrtec), (2) Decongestants: Pseudoephedrine (Sudafed), and (3) Glucocorticoid Nasal Sprays: Fluticasone (Flonase)

Immunomodulators:
Omalizumab (Xolair)

- Indication: Long-term control and prevention of symptoms in patients > 12 years old who have moderate-severe persistent allergic asthma inadequately controlled with ICS.
  - Omalizumab is administered every 2-4 weeks.
- MOA: Omalizumab binds to IgE → blocks IgE from binding to receptors on basophils and mast cells → decreases mast cell mediator release due to allergen exposure.
- Side Effects: pain and brusing on injection site (5-20%), malignant neoplasms (0.5%), anaphylaxis (0..5%).

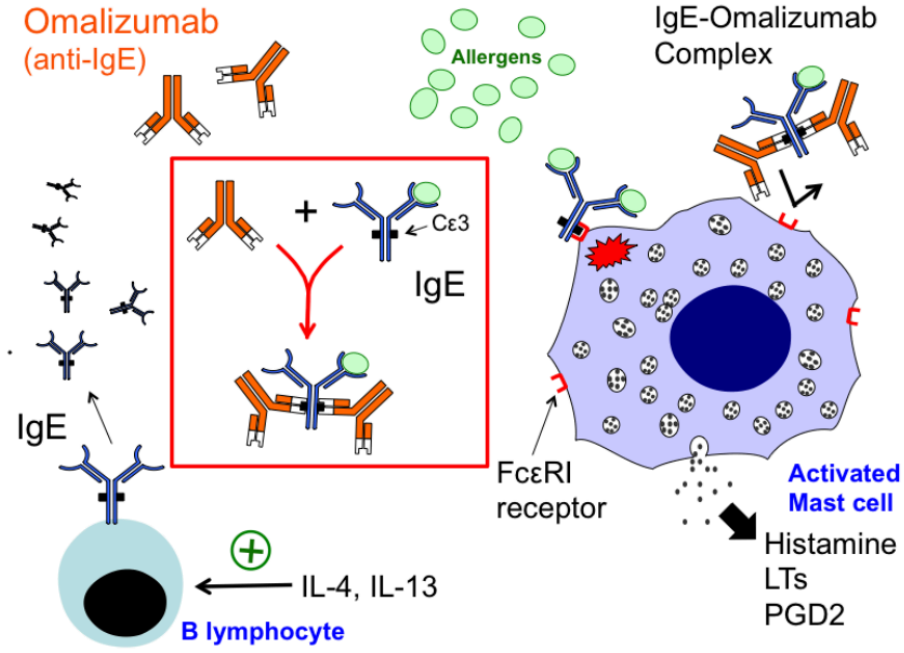


Figure 11. Omalizumab is a humanized monoclonal antibody that binds to the Cε3 domain of circulating IgE, which prevents IgE from binding to and activating receptors on mast cells and lymphocytes. In this illustration, a mast cell is used to illustrate the beneficial effects of omalizumab.

Asthma in Pregnancy

- The same stepped-care approach used for general asthma control is used for asthma control during pregnancy.
- No therapy has been proven absolutely safe for use during pregnancy → consideration is given to risks vs benefits.
- For pregnant patients requiring anti-inflammatory therapy, the use of beclomethasone or cromolyn inhalers is supported by human studies.
- Burst treatment with oral corticosteroids are appropriate for the treatment of asthma exacerbation because corticosteroid use in preferable to the deleterious physiologic effects of withholding treatment.

	Risk Factor Category According to Manufacturer's FDA Approved Product Labeling
Bronchodilator	
Albuterol	C
Metaproterenol	C
Terbutaline	B
Theophylline	C
Anti-inflammatory	
Cromolyn sodium	B
Beclomethasone dipropionate	C
Prednisone	(Not rated)
Flunisolide	C
Triamcinolone	D
Antihistamine	
Chlorpheniramine	B
Brompheniramine	C
Terfenadine	C
Astemizole	C
Triprolidine	B

Key to Risk Factor Ratings

Category

A **Controlled studies show no risk.** Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.

B **No evidence of risk in humans.** Either animal findings show risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative.

C **Risk cannot be ruled out.** Human studies are lacking, and animal studies are either positive for fetal risk, or lacking as well. However, potential benefits may justify the potential risk.

D **Positive evidence of risk.** Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.

X **Contraindicated in pregnancy.** Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk that clearly outweighs any possible benefit to the patient.

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
Corticosteroids (Glucocorticoids) ***Inhaled (ICS):*** Beclomethasone dipropionate Budesonide Flunisolide Fluticasone propionate Mometasone furoate Triamcinolone acetonide	*Indications* ■ Long-term prevention of symptoms; suppression, control, and reversal of inflammation. ■ Reduce need for oral corticosteroid. *Mechanisms* ■ **Anti-inflammatory.** Block late reaction to allergen and reduce airway hyperresponsiveness. Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation. ■ Reverse beta$_2$-receptor downregulation. Inhibit microvascular leakage.	■ Cough, dysphonia, oral thrush (candidiasis). ■ In high doses (see figures 4-4b and 4–8b), systemic effects may occur, although studies are not conclusive, and clinical significance of these effects has not been established (e.g., adrenal suppression, osteoporosis, skin thinning, and easy bruising) (Barnes and Pedersen 1993; Kamada et al. 1996). In low-to-medium doses, suppression of growth velocity has been observed in children, but this effect may be transient, and the clinical significance has not been established (CAMP 2000; Guilbert et al. 2006).	■ Spacer/holding chamber devices with nonbreath-activated MDIs and mouth washing after inhalation decrease local side effects. ■ Preparations are not absolutely interchangeable on a mcg or per puff basis (see figures 4–4b and 4–8b for estimated clinical comparability). New delivery devices may provide greater delivery to airways; this change may affect dose. ■ The risks of uncontrolled asthma should be weighed against the limited risks of ICS therapy. The potential but small risk of adverse events is well balanced by their efficacy. (See text.) ■ "Adjustable dose" approach to treatment may enable reduction in cumulative dose of ICS treatment over time without sacrificing maintenance of asthma control. ■ Dexamethasone is not included as an ICS for long-term control because it is highly absorbed and has long-term suppressive side effects.
Systemic: Methylprednisolone Prednisolone Prednisone	*Indications* ■ For short-term (3–10 days) "burst": to gain prompt control of inadequately controlled persistent asthma. ■ For long-term prevention of symptoms in severe persistent asthma: suppression, control, and reversal of inflammation. *Mechanisms* ■ Same as inhaled.	■ Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis. ■ Long-term use: adrenal axis suppression, growth suppression, dermal thinning, hypertension, diabetes, Cushing's syndrome, cataracts, muscle weakness, and—in rare instances—impaired immune function. ■ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, and *Strongyloides.*	■ Use at lowest effective dose. For long-term use, alternate-day a.m. dosing produces the least toxicity. If daily doses are required, one study shows improved efficacy with no increase in adrenal suppression when administered at 3 p.m. rather than in the morning (Beam et al. 1992).

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS (CONTINUED)

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
Cromolyn Sodium and Nedocromil	*Indications* ■ Long-term prevention of symptoms in mild persistent asthma; may modify inflammation. ■ Preventive treatment prior to exposure to exercise or known allergen. *Mechanisms* ■ **Anti-inflammatory.** Blocks *early* and late reaction to allergen. Interferes with chloride channel function. Stabilizes mast cell membranes and inhibits activation and release of mediators from eosinophils and epithelial cells. ■ Inhibits acute response to exercise, cold dry air, and SO_2.	■ Cough and irritation. ■ 15–20 percent of patients complain of an unpleasant taste from nedocromil.	■ Therapeutic response to cromolyn and nedocromil often occurs within 2 weeks, but a 4- to 6-week trial may be needed to determine maximum benefit. ■ Dose of cromolyn by MDI (1 mg/puff) may be inadequate to affect airway hyperresponsiveness. Nebulizer delivery (20 mg/ampule) may be preferred for some patients. ■ Safety is the primary advantage of these agents.
Immunomodulators			
Omalizumab (Anti-IgE) For subcutaneous use	*Indications* ■ Long-term control and prevention of symptoms in adults (≥12 years old) who have moderate or severe persistent allergic asthma inadequately controlled with ICS. *Mechanisms* ■ Binds to circulating IgE, preventing it from binding to the high-affinity (FcεRI) receptors on basophils and mast cells. ■ Decreases mast cell mediator release from allergen exposure. ■ Decreases the number of FcεRIs in basophils and submucosal cells.	■ Pain and bruising of injection sites has been reported in 5–20 percent of patients. ■ Anaphylaxis has been reported in 0.2 percent of treated patients. ■ Malignant neoplasms were reported in 0.5 percent of patients compared to 0.2 percent receiving placebo; relationship to drug is unclear.	■ Monitor patients following injection. Be prepared and equipped to identify and treat anaphylaxis that may occur. ■ The dose is administered either every 2 or 4 weeks and is dependent on the patient's body weight and IgE level before therapy. ■ A maximum of 150 mg can be administered in one injection. ■ Needs to be stored under refrigeration at 2–8 °C. ■ Whether patients will develop significant antibody titers to the drug with long-term administration is unknown.

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS (CONTINUED)

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
Leukotriene Receptor Antagonists (LTRAs)	*Mechanisms* ■ **Leukotriene receptor antagonist;** selective competitive inhibitor of $CysLT_1$ receptor.		■ May attenuate EIB in some patients, but less effective than ICS therapy (Vidal et al. 2001). ■ Do not use LTRA + LABA as a substitute for ICS + LABA.
Montelukast tablets and granules	*Indications* ■ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥1 year of age. May also be used with ICS as combination therapy in moderate persistent asthma.	■ No specific adverse effects have been identified. ■ Rare cases of Churg-Strauss have occurred, but the association is unclear.	■ A flat dose-response curve, without further benefit, if dose is increased above those recommended.
Zafirlukast tablets	■ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥7 years of age. May also be used with ICS as combination therapy in moderate persistent asthma.	■ Postmarketing surveillance has reported cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplantation.	■ Administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ■ Zafirlukast is a microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin. INRs should be monitored during coadministration. ■ Patients should be warned to discontinue use if they experience signs and symptoms of liver dysfunction (right upper quadrant pain, pruritis, lethargy, jaundice, nausea), and patients' ALTs should be monitored.
5-Lipoxygenase Inhibitor	*Mechanisms* ■ Inhibits the production of leukotrienes from arachidonic acid, both LTB_4 and the cysteinyl leukotrienes.		
Zileuton tablets	*Indications* ■ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥12 years of age. ■ May be used with ICS as combination therapy in moderate persistent asthma in patients ≥12 years of age.	■ Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia.	■ Zileuton is microsomal P450 enzyme inhibitor that can inhibit the metabolism of warfarin and theophylline. Doses of these drugs should be monitored accordingly. ■ Monitor hepatic enzymes (ALT).

FIGURE 3–22. LONG-TERM CONTROL MEDICATIONS (CONTINUED)

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
Long-Acting Beta$_2$-Agonists (LABA) *Inhaled LABA:* Formoterol Salmeterol	*Indications* ■ Long-term prevention of symptoms, added to ICS ■ Prevention of EIB. ■ *Not to be used to treat acute symptoms or exacerbations.* *Mechanisms* ■ **Bronchodilation.** Smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP, producing functional antagonism of bronchoconstriction. ■ Compared to SABA, salmeterol (but not formoterol) has slower onset of action (15–30 minutes). Both salmeterol and formoterol have longer duration (>12 hours) compared to SABA.	■ Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QTc interval in overdose. ■ A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established. ■ Potential risk of uncommon, severe, life-threatening or fatal exacerbation; see text for additional discussion regarding safety of LABAs.	■ Not to be used to treat acute symptoms or exacerbations. ■ Should not be used as monotherapy for long-term control of asthma or as anti-inflammatory therapy. ■ May provide more effective symptom control when added to standard doses of ICS compared to increasing the ICS dosage. ■ Clinical significance of potentially developing tolerance is uncertain, because studies show symptom control and bronchodilation are maintained. ■ Decreased duration of protection against EIB may occur with regular use.
Oral: Albuterol, sustained-release			■ Inhaled route is preferred because LABAs are longer acting and have fewer side effects than oral sustained-release agents. Oral agents have not been adequately studied as adjunctive therapy with ICS.
Methylxanthines Theophylline, sustained-release tablets and capsules	*Indications* ■ Long-term control and prevention of symptoms in mild persistent asthma or as adjunctive with ICS, in moderate or persistent asthma. *Mechanisms* ■ **Bronchodilation.** Smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism. ■ May affect eosinophilic infiltration into bronchial mucosa as well as decreases T-lymphocyte numbers in epithelium. ■ Increases diaphragm contractility and mucociliary clearance.	■ Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia. ■ Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, difficulty in urination in elderly males who have prostatism.	■ Maintain steady-state serum concentrations between 5 and 15 mcg/mL. Routine serum concentration monitoring is essential due to significant toxicities, narrow therapeutic range, and individual differences in metabolic clearance. Absorption and metabolism may be affected by numerous factors which can produce significant changes in steady-state serum theophylline concentrations. ■ Patients should be told to discontinue if they experience toxicity. ■ Not generally recommended for exacerbations. There is minimal evidence for added benefit to optimal doses of SABA. Serum concentration monitoring is mandatory.

Key: anti-IgE, anti-immunoglobulin E, EIB, exercise-induced bronchospasm; INR, International Normalized Ratio; LABA, long-acting beta$_2$-agonist; MDI, metered-dose inhaler; SABA, inhaled short-acting beta$_2$-agonist

FIGURE 3–23. QUICK-RELIEF MEDICATIONS

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Short-Acting Beta$_2$-Agonists (SABA) *Inhaled SABA:* Albuterol Levalbuterol Pirbuterol	*Indications* ■ Relief of acute symptoms; quick-relief medication. ■ Preventive treatment for EIB prior to exercise. *Mechanisms* ■ **Bronchodilation.** Binds to the beta$_2$-adrenergic receptor, producing smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP producing functional antagonism of bronchoconstriction.	■ Tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, hyperglycemia. Inhaled route, in general, causes few systemic adverse effects. Patients with preexisting cardiovascular disease, especially the elderly, may have adverse cardiovascular reactions with inhaled therapy.	■ Drugs of choice for acute bronchospasm. Inhaled route has faster onset, fewer adverse effects, and is more effective than systemic routes. The less beta$_2$-selective agents (isoproterenol, metaproterenol, isoetharine, and epinephrine) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses. Oral systemic beta$_2$-agonists are not recommended. ■ For patients who have intermittent asthma, regularly scheduled daily use neither harms nor benefits asthma control (Drazen et al. 1996). Regularly scheduled daily use is not recommended. ■ Regular use >2 days/week for symptom control (not prevention of EIB), increasing use, or lack of expected effect indicates inadequate asthma control. ■ For patients frequently using SABA, anti-inflammatory medication should be initiated or intensified. ■ Levalbuterol at one-half the mcg dose produces clinically comparable bronchodilation and systemic side effects as racemic albuterol.

FIGURE 3–23. QUICK-RELIEF MEDICATIONS (CONTINUED)

Name/Products	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues
Anticholinergics Ipratropium bromide	*Indications* ■ Relief of acute bronchospasm (See Therapeutic Issues column.). *Mechanisms* ■ **Bronchodilation.** Competitive inhibition of muscarinic cholinergic receptors. ■ Reduces intrinsic vagal tone of the airways. May block reflex bronchoconstriction secondary to irritants or to reflux esophagitis. ■ May decrease mucous gland secretion.	■ Drying of mouth and respiratory secretions, increased wheezing in some individuals, blurred vision if sprayed in eyes. If used in the ED, produces less cardiac stimulation than SABAs.	■ Reverses only cholinergically mediated bronchospasm; does not modify reaction to antigen. Does not block EIB. ■ Multiple doses of ipratropium in the ED provide additive effects to SABA. ■ May be alternative for patients who do not tolerate SABA. ■ Treatment of choice for bronchospasm due to beta-blocker medication. ■ Has not proven to be efficacious as long-term control therapy for asthma.
Corticosteroids *Systemic:* Methylprednisolone Prednisolone Prednisone	*Indications* ■ For moderate or severe exacerbations to prevent progression of exacerbation, reverse inflammation, speed recovery, and reduce rate of relapse. *Mechanisms* ■ **Anti-inflammatory.** See figure 3–22.	■ Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, facial flushing, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis. ■ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, and *Strongyloides.*	■ Short-term therapy should continue until patient's symptoms resolve. This usually requires 3–10 days but may require longer. — Action may begin within an hour. ■ There is no evidence that tapering the dose following improvement is useful in preventing a relapse in asthma exacerbations. ■ Other systemic corticosteroids such as hydrocortisone and dexamethasone given in equipotent daily doses are likely to be as effective as prednisolone.

Key: ED, emergency department; EIB, exercise-induced bronchospasm

Long-Term Asthma Controller Medications: LTRAs & Combined ICS + LABA (UpToDate)

Medication	Dose form	0 to 4 years	5 to 11 years	Comments
Leukotriene receptor antagonists (LTRAs)[¶]				
Montelukast	4 mg or 5 mg chewable tablet 4 mg granule packets	4 mg once daily at bedtime (1 to 5 years of age).	5 mg once daily at bedtime (6 to 14 years of age).	When LTRA treatment is indicated, montelukast is preferred.
Zafirlukast	10 mg tablet	Safety and efficacy not established.	10 mg twice per day on empty stomach.	Zafirlukast has potential drug interactions and a small risk of hepatotoxicity. Food decreases bioavailability of zafirlukast; take at least 1 hour before or 2 hours after meals.
Combined inhaled glucocorticoids and long-acting beta agonists (LABAs)[Δ]				
Fluticasone-salmeterol	DPI 100 mcg/50 mcg	Safety and efficacy not established.	1 inhalation twice per day.	Most children <4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery of DPI.
	MDI 45 mcg/21 mcg		2 puffs twice per day.	Do not exceed dose shown.
Budesonide-formoterol	HFA MDI 80 mcg/4.5 mcg	Safety and efficacy not established.	1 to 2 puffs twice per day.	Onset of formoterol is similar to albuterol.
Mometasone-formoterol	HFA MDI 50 mcg/5 mcg	Safety and efficacy not established.	2 puffs twice per day.	There have been no clinical trials in children ≤4 years of age. Do not exceed dose shown.

Long-Term Asthma Controller Medications: Systemic Glucocorticoids, LAMAs, Chromes, & Theophylline

Systemic glucocorticoids				
Methylprednisolone Prednisolone Prednisone	For detail, refer to Lexicomp drug-specific monographs included with UpToDate	0.25 to 2 mg/kg orally per day or every other day given in the morning. Titrate to the lowest acceptable dose that maintains control.	0.25 to 2 mg/kg orally per day or every other day given in the morning. Titrate to the lowest acceptable dose that maintains control.	**(Applies to all 3 glucocorticoids)** Due to their toxic effects, systemic glucocorticoids should be used only rarely for long-term control of asthma (ie, in those few patients with poorly controlled severe persistent asthma despite compliance with maximized ICS and other pharmacologic and preventive therapies). Refer to UpToDate topics on the treatment of persistent asthma in children. The use and dosing of systemic glucocorticoids for the treatment of acute asthma exacerbations is reviewed elsewhere. Refer to UpToDate topics on acute asthma exacerbations in children in the emergency department and inpatient management.
Long-acting anticholinergic agents				
Tiotropium	Soft-mist inhaler 1.25 mcg/actuation	Safety and efficacy not established.	2 inhalations once daily. (Off-label use: 2 inhalations of 2.5 mcg/actuation dose once daily.)	Inhaler is used without a spacer/valved holding chamber. There have been no clinical trials in children ≤4 years of age.
Chromones				
Cromolyn sodium (sodium cromoglycate)	5 mg/puff CFC free MDI (not available in the United States)[◇]	Safety and efficacy not established	2 puffs 4 times per day.	Less effective than ICS in children. Add-on to ICS is not recommended. Refer to UpToDate topics on the treatment of persistent asthma in children. 4- to 6-week trial may be needed to determine maximum benefit. May cause bronchospasm. Premedication with bronchodilator may be needed. Use of spacer device may substantially decrease amount of drug delivered. Once control is achieved, the frequency of dosing may be reduced.
	20 mg/ampule solution for nebulization	20 mg 4 times per day. Safety and efficacy not established in children aged <2 years.	20 mg 4 times per day.	
Nedocromil	2 mg/puff CFC free inhaler (not available in the United States)[◇]	Safety and efficacy not established in children aged <6 years.	2 puffs 4 times per day.	
Biologic agents: Refer to separate UpToDate table and topics on biologic therapy for asthma, including omalizumab (anti-IgE) and mepolizumab (anti-IL-5)				
Methylxanthines				
Theophylline	Liquids, sustained-release tablets and capsules	Starting dose for patients without risk factors for decreased theophylline clearance approximately 10 mg/kg per day (initial maximum 300 mg per day). Usual maximum following titration: ▪ <1 year of age: 0.2 × (age in weeks) + 5 = dose in mg/kg per day ▪ ≥1 year of age: 16 mg/kg per day (maximum 600 mg per day)	Starting dose for patients without risk factors for decreased theophylline clearance approximately 10 mg/kg/day (initial maximum 300 mg per day). Usual maximum following titration: ▪ 16 mg/kg/day (maximum 600 mg per day)	Due to risk of toxic effects, requirement of frequent serum concentration monitoring, and significant drug-drug interactions, theophylline is infrequently used. Monitoring and dose adjustment is required to maintain peak serum levels of 5 to 15 mcg/mL at steady-state. For additional information, including approach to dose adjustment, refer to UpToDate topics on theophylline use in asthma.