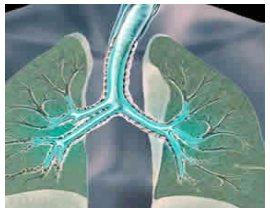
DRUGS AFFECTING THE RESPIRATORY SYSTEM

Pharmacotherapy of bronchial asthma



DRUGS ACTING ON THE RESPIRATORY SYSTEM

- **ANTITUSSIVES AND EXPECTORANTS**

- **BRONCHODILATORES:**

- beta receptor agonists
- anticholinergics
- methyl xanthine derivatives

- **ANTI-INFLAMMATORY AGENTS:**

- corticosteroids, antileukotrienes, mast cell stabilizers, antihistamines, biological drugs for asthma

Cough Physiology

Cough reflex

Initiated by irritation of sensory receptors in the respiratory tract

Induces coughing and expectoration

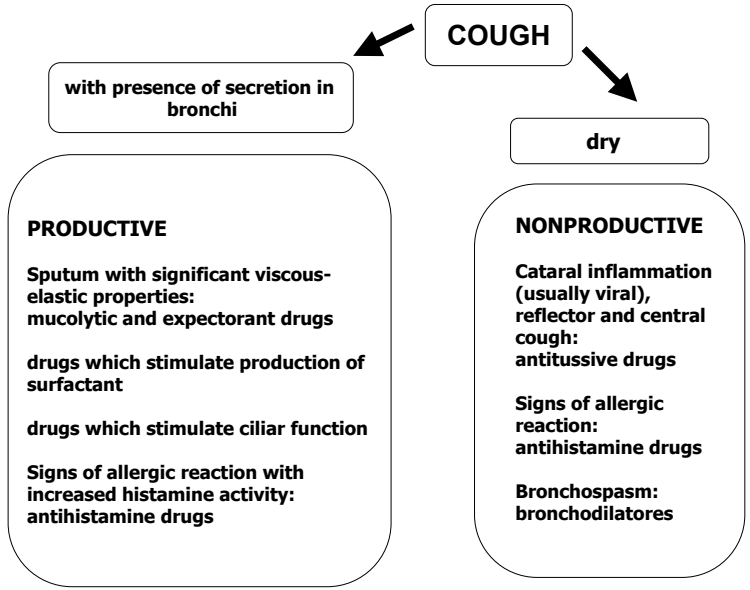
Most of the time, coughing is beneficial:

- **Removes excessive secretions**
- **Removes potentially harmful foreign substances**

In some situations, coughing can be harmful (such as after hernia repair surgery)

Basic Types of Cough

- **Productive cough:** congested, removes excessive secretions
- **Nonproductive cough:** dry cough



ANTITUSSIVES

- drugs used to stop or reduce coughing
- used only to stop the cough reflex when the cough is nonproductive and/or harmful
- **Centrally acting:**

  Opioid drugs (codeine, hydrocodone, dextromethorphan)

  Nonopioid drugs (butamirate)
- **Peripherally acting** (levodropropizine)

Mechanism of action of opioid antitussives

Opioids

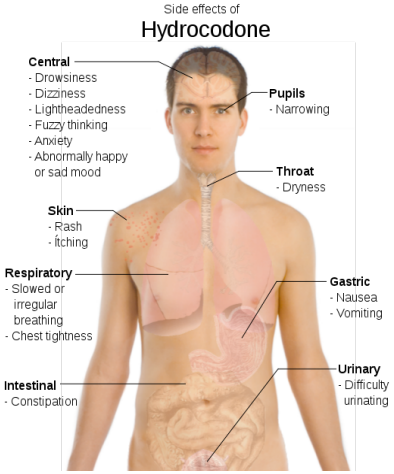
- **centrally acting**
- **Suppress the cough reflex by direct action on the cough centre in the medulla**
- Opioid analgesics are **the most effective drugs** available for the suppression of cough
- This effect is often achieved at doses below those necessary to produce analgesia

CODEINE

- Codeine (methylmorphine)
- Considerably less addiction liability (compared to opioid analgesic)
- Has a useful antitussive action at doses lower than those required for analgesia
- 15 mg is usually sufficient to relieve cough
- Decreases secretions in the bronchioles, inhibits ciliary activity
- Enhances the effect of NSAID (acetaminophen--paracetamol/ibuprofen/codeine)
- Side effects: constipation, some respiratory depression

Hydrocodone

- Hydrocodone (synthetic) is more potent antitussive than codeine
- Less respiratory suppressant
- **Addictive properties like codeine**
- acetaminophen/ hydrocodone (VICODIN)



Side Effects of opioid antitussives

- **CNS and respiratory depression**
- **Addictive potential**
- Sedation
- Nausea, vomiting
- Lightheadedness
- **Constipation** because of action of opiates on the GI tract

Dextromethorphan

- **Dextrorotatory stereoisomer** of a methylated derivative of levorphanol (synthetic opioid analgesic)
- Antitussive potency is equivalent to codeine
- **Free of analgesic and addictive properties**
- **Does not cause CNS or respiratory depression**
- Produces less constipation than codeine
- May produce dizziness, drowsiness, nausea
- Usual antitussive dose 15-30mg 3-4 times daily
- Available in many over-the-counter products
- Drug interaction: with MAOI (dextromethorphan may increase releasing of serotonin)

Butamirate

- **nonopioid** antitussive
- **suppress the cough reflex by direct action on the cough centre in the medulla**
- **also relax bronchial smooth muscle**
- antitussive potency similar to codeine
- vailable in over-the-counter products
- **side effects:** drowsiness, dizziness, nausea, diarrhea, itchy skin rash
- suitable for children>8 months of age

Peripheral Antitussives Mechanism of Action

- **Suppress the cough reflex by numbing the stretch receptors in the respiratory tract and preventing the cough reflex from being stimulated**

Benzonatate

- **Suppresses cough through a peripheral action, anesthetizing the stretch or cough receptors of vagal afferent fibers, which are located in the respiratory passages, lungs, and pleura**
- May suppress transmission of the cough reflex by a **central mechanism**, at the level of the medulla
- **Local anesthetic activity** when applied topically to the mucosa
- It is used to provide relief of acute cough due to minor throat and bronchial irritation occurring with colds or inhaled irritants
- **Side effects:** dizziness, headache, sedation

Levodropropizine

- **acts as a peripheral antitussive (supress receptors in the bronchi and trachea)**, with no action in the central nervous system
- shows anti-allergic activity (antihistamine action), may inhibit bronchospasm
- does not cause side effects such as constipation or respiratory depression
- may cause nausea, vomiting, heartburn, diarrhea, fatigue, weakness, drowsiness, dizziness, headache

EXPECTORANT drugs

- **Drugs that aid in the expectoration (removal) of mucus** - non-specific treatment of cough
- **Cough is blocked peripherally by removing irritants**

2 groups of expectorant drugs:

1. **drugs that increase the volume of secretions -** secretolytics **- mucokinetic drugs**
2. **drugs that reduce the viscosity of secretions** (disintegrate and thin secretions) **- mucolytic drugs**

EXPECTORANTS
Mucokinetic drugs

mechanism of action of mucokinetics:

- Direct stimulation
- Reflex stimulation
- Changing pH - the change in pH liquefies the secretion (increasing or decreasing in pH of secretion): saline expectorants, sodium bicarbonate, ammonium chloride

Reflex stimulation

- Agent causes irritation of the GI tract
- Loosening and thinning of respiratory tract secretions occur in response to this irritation
  - Example: **guaifenesin** (creosote compounds)

Direct stimulation

- The secretory glands are stimulated directly to increase their production of respiratory tract fluids
  - Examples: **iodine-containing products** such as iodinated glycerol and potassium iodide, **essential oils** inhalation

EXPECTORANTS

Mucolytic Drugs

- **Facilitate removal of viscous and inspissated pulmonary secretion (chronic)**
- **Improve ciliary activity, mobilize secretions by changing viscosity**

Viscosity is decreased by:

- **Rupturing disulfide bond of the mucus**
- **steins derivatives: acetylcysteine, carbocisteine, erdosteine**
- **mesna, bromhexine, ambroxol**

Acetylcysteine

- **Commonly administred orally** (PO)
- **Disrupts the disulfide bond of the mucoprotein to small fragments**
- **Acetylcysteine stimulates respiratory secretions**
- **Improves antibiotic absorption and gas exchange**
- Metabolized in the liver to amino acids cysteine and cystine
- **Used in** bronchitis, tobacco smoke, COPD, cystics fibrosis, asthma, TB, pneumonia, emphysema & adult respiratory distress syndrome
- **Used in acetaminophen (paracetamol) overdose** (IV)
- **Side effects: vomiting, anorexia, reflex bronchoconstriction through irritant receptors**

Carbocisteine

- **mucolytic agent for the adjunctive therapy of respiratory tract disorders** characterised by excessive, viscous mucus, including chronic obstructive airways disease
- prevents pulmonary infections by decreasing accumulated mucus in the respiratory tract; this is especially beneficial in preventing exacerbations of COPD caused by bacteria and viruses
- for oral use (tablets, capsules or syrups)
- **side effects:** diarrhoea, nausea, epigastric discomfort and gastrointestinal bleeding, skin rashes and allergic skin eruptions

Erdosteine

- **orally use mucolytic agent** (capsules, suspension)
- **inhibit some inflammatory mediators** and some pro-inflammatory cytokines that are specifically involved in oxidative stress
- antitussive effects may be regarded as related to its anti-inflammatory properties via the improvement of mucociliary clearance and the reduction of chemokines from epithelial cells
- three active metabolites result and possess **mucolytic activity in addition to free radical scavenging activity**
- mild gastrointestinal side effects

Mesna

- **Mucolytic agent:**
  working in the same way as acetylcysteine
  (used only in aerosol form)
- **Chemotherapy adjuvant:**

- used to reduce the incidence of haemorrhagic cystitis and haematuria when a patient receives ifosfamide or cyclophosphamide for cancer chemotherapy (these two anticancer agents, in vivo, may be converted to urotoxic metabolites such as acrolein)
- Mesna assists to neutralise these metabolites by binding through its sulfhydryl-moieties, and also increases urinary excretion of cysteine (given IV)

Bromhexine

- **mucolytic** and expectorant **mucokinetic** agent used in the treatment of respiratory disorders associated with viscid or excessive mucus
- **disrupts the disulfide bond of the mucoprotein**
- **stimulates surfactant synthesis**

(surfactant acts as an anti-glue factor by reducing the adhesion of mucus to the bronchial wall, in improving its transport and in providing protection against infection and irritating agents)

• oral administration (PO - syrups, tablets)

Ambroxol

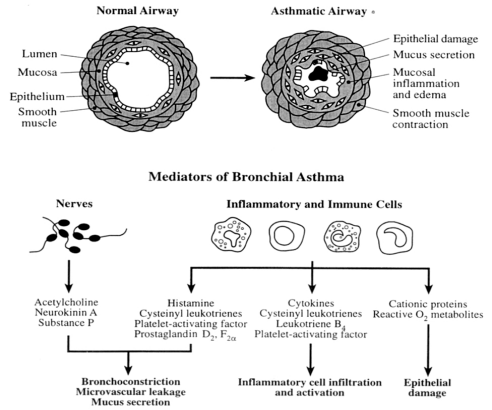
- active metabolite of bromhexine
- **decrease the viscosity of mucus by splitting the disulfide bonds of mucoproteins**
- **stimulates synthesis and release of surfactant**
- exhibit **the local anaesthetic effect** (provides pain relief in acute sore throat)
- is also **anti-inflammatory**, reducing redness in a sore throat (lozenges)
- used orally (PO) and in inhaled form

PHARMACOTHERAPY of bronchial asthma

Asthma definition

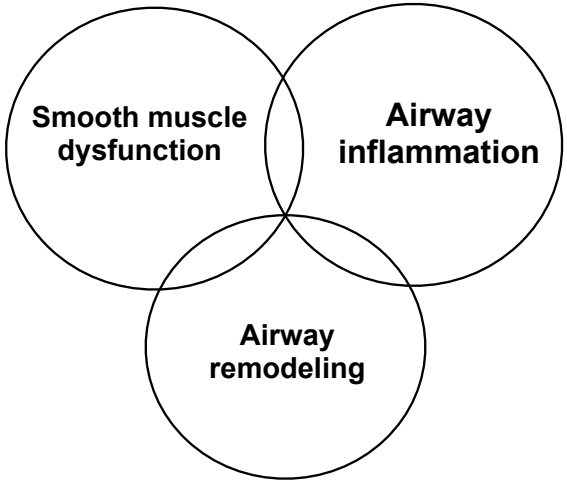
- **CHRONIC INFLAMMATORY disease of the airways causing REVERSIBLE airflow obstruction**
- characterized by ACUTE episodes or „attacks" such as:
  - coughing (may be the only symptom)
  - wheezing
  - chest tightness
  - **dyspnea** – difficulty breathing
- not contagious
- can be controlled, but not cured
- >80% of asthmatics have allergies

Central characteristic of asthma



- **Airway Inflammation** is central to the pathogenesis of asthma
- **Bronchial Hyperreactivity** abnormal sensitivity to various stimuli - trigger
- **Bronchospasm (intermittent airflow obstruction)** can be treated with bronchodilators, acutely

Asthma pathophysiology



Two main pathophysiologic types of asthma

1. Extrinsic asthma (allergic asthma)

- common in children, associated with a genetic predisposition and is precipitated by a known **allergens**
- it is related to the formation of antibody **IgE** in the body

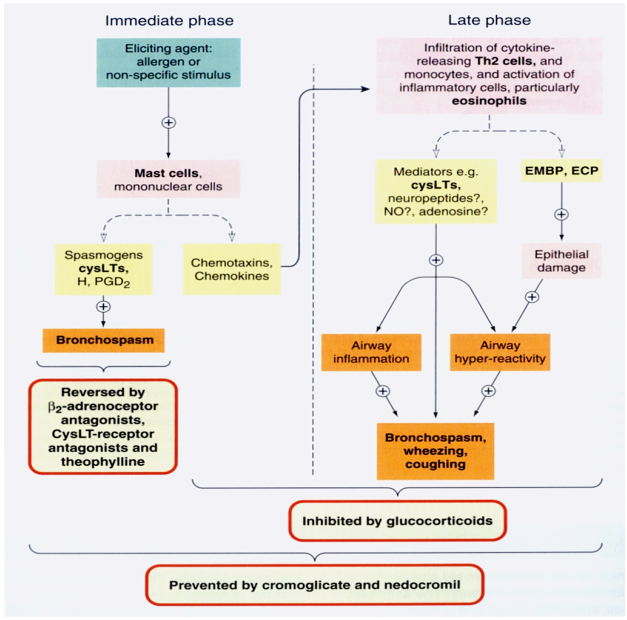
2. Intrinsic asthma (non allergic asthma)

- tend to develop in adulthood, and symptoms are triggered by **non-allergic factors** such as:

✓ viral infection, irritants which cause epithelial damage and mucosal inflammation

✓ emotional upset which mediates excess parasympathetic input

✓ exercise which causes water and heat loss from the airways



Drugs used to treat asthma

- Categories of antiasthmatic drugs:

1. **BRONCHODILATORS**
2. **ANTI-INFLAMMATORY AGENTS**
3. ANTI-INFLAMMATORY RELIEVER (ICS/Formoterol)

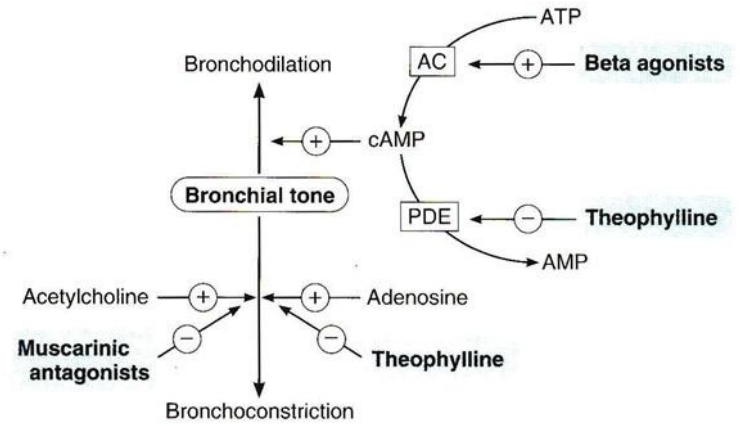
- **bronchodilators are effective in reversing the bronchospasm of the immediate phase**
- **anti-inflammatory agents are effective in inhibiting or preventing the inflammatory components of both phases**

BRONCHODILATORS

provide short-term relief

- **β2-ADRENOCEPTOR AGONISTS**
- **MUSCARINIC RECEPTOR ANTAGONISTS**
- XANTHINE DRUGS

Bronchodilators sites of action



ANTI-INFLAMMATORY AGENTS

reduce bronchial hyperactivity and protect against cellular infiltration

- **GLUCOCORTICOIDS**
- **LEUKOTRIENE MODIFIERS (LTRA)**
- HISTAMINE H1-RECEPTOR ANTAGONISTS
- **ANTI-IgE monoclonal ANTIBODIES**
- **ANTI-IL-5, IL-5R, IL-4 THERAPY**

SHORT-TERM CONTROL MEDS

Quick relief (reliever medications)

- EXACERBATIONS ONLY

- Prompt relief of bronchoconstriction and acute symptoms such as cough, chest tightness and wheezing
- Onset of action 5-10 min - 4 hours
  - **SHORT ACTING BETA 2 AGONISTS** (SABA)
  - **ANTICHOLINERGICS** (SAMA)
  - **SYSTEMIC CORTICOSTEROIDS**

LONG-TERM CONTROL MEDS

- INHALED:

- **CORTICOSTEROIDS** (ICS)
- **LONG ACTING BETA 2 AGONISTS** (LABA)

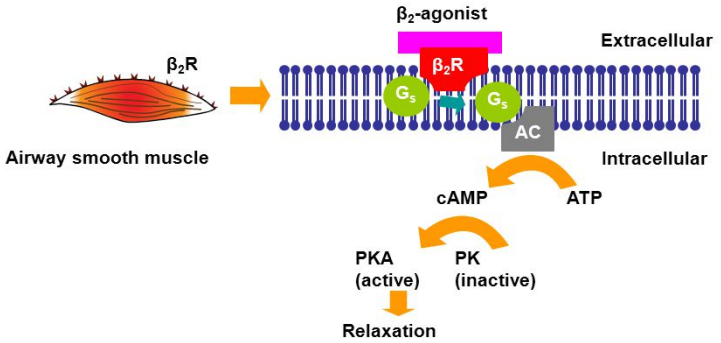
- ADMINISTRED ORALLY:

- **LEUKOTRIENE MODIFIERS**
- METHYLXANTHINES: theophylline

Bronchodilators
β2-ADRENOCEPTOR AGONISTS

- **Stimulate beta$_2$-adrenergic bronchial receptors: increased cAMP and decreased intracellular calcium**
- **Relaxes muscles in the airways** to help relieve asthma symptoms (quickly reduce airway constriction and restore normal airflow)
- Inhibit mediator release from mast cells and the release TNF-α from monocytes
- Selective drugs are prefer in asthma (lower side effects, without cardiac stimulation)
- Inhalation of aerosol, powder or nebulised solution results in the greatest local effect on airway smooth muscle with the least systemic toxicity

Mechanism of action of β_2-agonists



- Stimulation of β_2-adrenoreceptors results in activation of adenylate cyclase, increased intracellular cAMP and subsequent airway smooth muscle relaxation

Bronchodilators
β2-ADRENOCEPTOR AGONISTS

- **Short-acting agents (SABA):**
  salbutamol (albuterol)**, fenoterol**
  given by inhalation
  maximum effect occurs within 30 min
  duration of action 4-6 hours
- **Long-acting agents (LABA):**
  salmeterol, formoterol (onset of action 2-3 min)
  given by inhalation
  duration of action 12 hours
- (uLABA): indacaterol, vilanterol, olodaterol 24 hours, COPD

Inhaled SABA
Therapeutic issues?
Potential adverse effects?

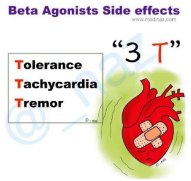
Therapeutic issues

- ✓ **Drugs of choice for acute bronchospasm in children,** second-line therapy in adults (other reliever option)
- ✓ **low dose ICS/FORMOTEROL is actually PREFERRED RELIEVER therapy in acute asthma attacks - (GINA 2023)**
- ✓ For relief of **acute symptoms** or **as preventive treatment** prior to exercise

Potential adverse effects

- ✓ Tremors, tachycardia, headache

Inhaled LABA
Therapeutic issues?
Potential adverse effects?



Therapeutic issues

- ✓ Should not be used in place of anti-inflammatory therapy
- ✓ Prevent bronchospasm (night-time attack)

Potential adverse effects

- ✓ **Tachycardia**, **tremors**, hypokalemia, nervousness, **development of tolerance**

β2-ADRENOCEPTOR AGONISTS SIDE EFFECTS

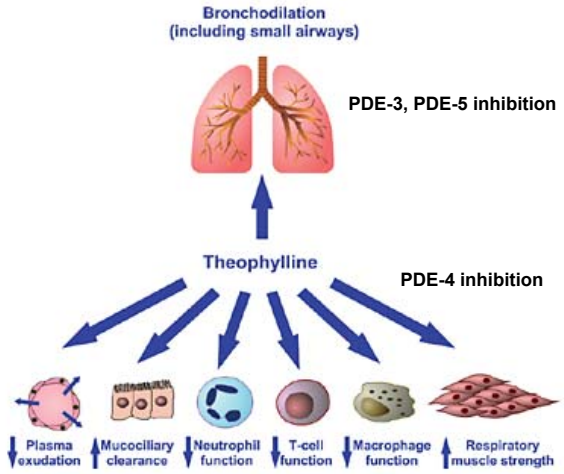
- CV: **tachycardia, arrythmias**, vascular headaches
- CNS: dizziness, nervousness
- **Skeletal muscle tremor**
- **Contraindicated**: clients with tachyarythmias, severe cardiac disease
- **Development of tolerance** – **tachyphylaxis** (steroids inhibit β2-adrenoceptor downregulation)

Bronchodilators
METHYL XANTHINE DERIVATIVES
THEOPHYLLINE Mechanism of action

- **Mechanism of action:**

  Inhibit phosphodiesterase (theophylline is nonspecific inhibitor of PDE isozymes in bronchial smooth muscle and inflammatory cells)

  Increased levels of cAMP result in bronchodilation (PDE-3 i PDE-5 inhibition) and **reduction of inflammatory mediators** (PDE-4 inhibition)
- Act as competitive **antagonists of adenosine** at adenosine receptors to prevent bronchoconstriction



THEOPHYLLINE doses

- Theophylline is the most effective **bronchodilator**
- **Inhibit the late phase of asthma**
- Improvement in pulmonary function is correlated with plasma concentration in **the range of 5-20 µg/ml**
- Anorexia, nausea, vomiting, abdominal discomfort, headache, and anxiety occur at concentrations of 15 µg/ml
- Higher levels (>40 µg/ml) may cause seizures or arrhythmias
- **Theophylline drugs are given orally in sustained-release preparations**
- Theophylline can also be given by slow intravenous injection - NOT RECOMMENDED

Theophylline - side effects

- Requires measurements of plasma levels when is given IV for treatment of status asthmaticus (currently NOT recommended) and to optimise therapy at high PO doses
- **Small therapeutic index** of theophylline: serum blood levels need to be monitored - side effects may occur at concentrations >15 µg/ml
- CV effects: dysrhythmia (>40 µg/ml)
- CNS: nervousness and tremor, headache, insomnia
- Gastrointestinal symptoms: anorexia, nausea, vomiting, diarrhea
- Interaction with drugs that inhibit or increase P450 enzymes

Clinical use of theophylline limited use

- As a second-line drug, in patients whose asthma does not respond adequately to CS+LABA+LAMA (night-time asthma)
- Intravenously in acute severe asthma (status asthmaticus) NOT RECOMMENDED
- **Long-term control of reversible airway obstruction caused by asthma or COPD** (sustained-release preparations; PO)

MUSCARINIC RECEPTOR ANTAGONISTS
Mechanism of action

- Acetylcholine (ACh) causes bronchial constriction and narrowing of the airways
- Anticholinergics bind to the ACh receptors in bronchial smooth muscle, resulting in decreased levels of cGMP
- Result: bronchoconstriction is prevented, airways dilate
- Antimuscarinic drugs cause bronchodilation by blocking cholinergic constrictor tone, act primarily in large airways
- **Selective M3 receptor antagonists** in the airways used as anti-asthmatic:

  IPRATROPIUM bromide (SAMA) duration of action 3-5 hours

  TIOTROPIUM bromide (LAMA) 24 hours duration of action

  glycopyrronium bromide; umeclidinium bromide >24 h (uLAMA) - valuable in patient with COPD

Muscarinic receptor antagonists Clinical use

- Given by aerosol inhalation
- Relaxes bronchial constriction caused by parasympathetic stimulation, which occurs particularly in asthma produced by irritant stimuli and can occur in allergic asthma
- **As an adjunct to β2 adrenoceptor agonists and steroids when these on their own do not control asthma** (salbutamol/ipratroprium; fenoterol/ipratropium)
- As a bronchodilators in some patients with chronic bronchitis
- Used to **prevent** bronchoconstriction
- **NOT used for acute asthma exacerbations!**

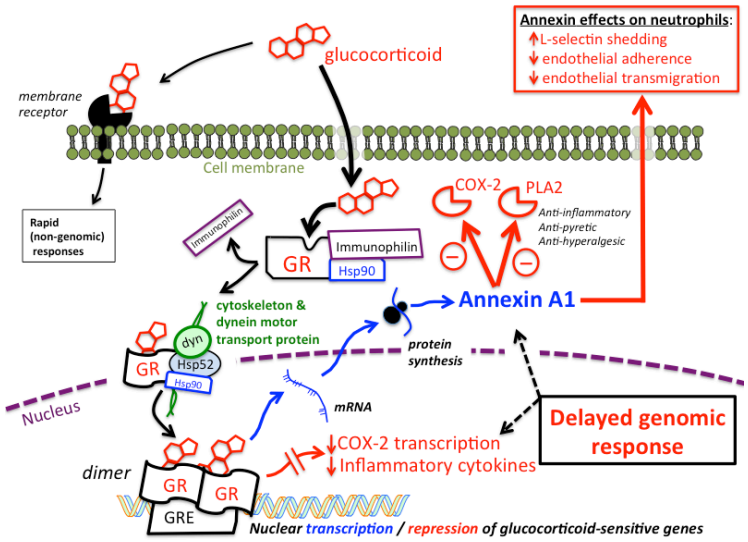
Muscarinic receptor antagonists
Side effects

- **Safe, well tolerated, few unwanted effects**
- **May produce anticholinergic activity** (LAMA):
  dry mouth or throat
  blurred vision
  urinary retension, constipation
  headache
  tachycardia
  No known drug interactions

GLUCOCORTICOIDS

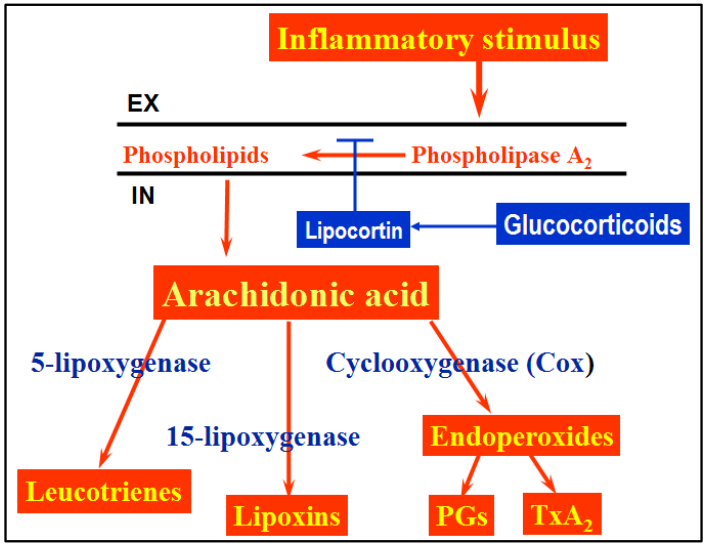
- Long-term control medications
- **Recommended for all intensity levels of asthma**
- GC have multiple effects that **decrease the inflammation in asthma**
- Do not relax airway smooth muscle directly but **reduce bronchial reactivity,** reduce the frequency of asthma exacerbations
- **Do not relieve symptoms of acute asthmatic attacks** (low dose ICS/FORMOTEROL is actually PREFERRED RELIEVER therapy in acute asthma attacks - GINA 2023)
- **Inhaled forms reduce systemic effect**

Glucocorticoids Mechanism of action



GLUCOCORTICOIDS
Mechanism of action

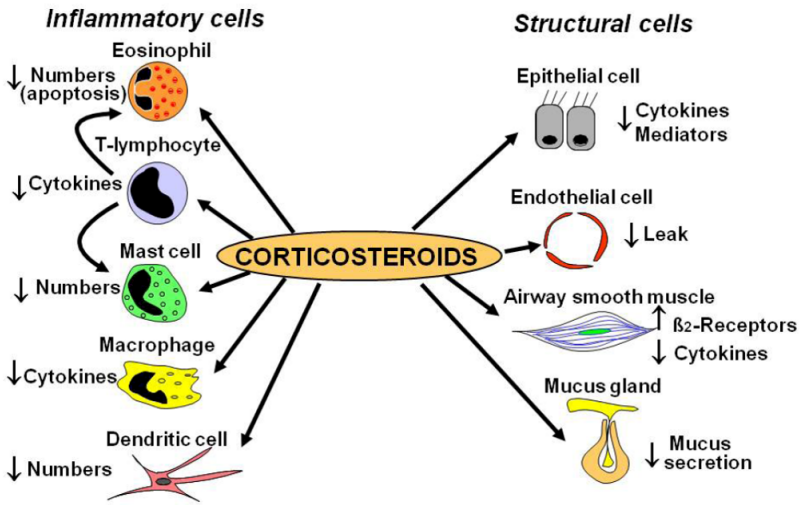
- act on glucocorticoid receptors (GR)
- **membrane glucocorticoid receptor: rapid, non-genomic response**
- **intracellular glucocorticoid receptor: delayed genomic response**
- Glucocorticoids reduce inflammation through a combination of both **inhibition & upregulation of gene transcription**
- **CS inhibit:** cyclooxygenase COX-2, lipooxygenase, inducible NOS, most inflammatory cytokines production
- **CS upregulated:** expression of β-adrenergic receptors and annexin A1 (lipocortin) - inhibition of prostaglandin and leukotriene production, post-transcriptional activity of COX-2, neutrophil penetration



GLUCOCORTICOIDS

Mechanism of action in pulmonary disorders

- **Control of eosinophils**
  margination of circulating eosinophils, decreased bone marrow production, reduced local recruitment
- **Reduced mucosal edema**
  decreased vascular permeability secondary to vasoconstriction
- **Increased synthesis and sensitivity of β-adrenergic receptor**



Clinical use of glucocorticoids in asthma

Inhaled corticosteroids

- Treatment of bronchospastic disorders with beta agonists
- Recommended for all intensity levels of asthma - long-term control meds
- NOT considered first-line agents for management of acute asthmatic attacks
- **low dose ICS/FORMOTEROL** (budesonide/formoterol) **is actually PREFERRED RELIEVER therapy in acute asthma attacks -** GINA 2023

Clinical use of glucocorticoids in asthma
Oral glucocorticoids

- **Chronic asthma** and **severe or rapidly deteriorating asthma** (short course of prednisolone)
- **Combined with an inhaled steroid to reduce the oral dose**

Clinical use of glucocorticoids in asthma
IV injectiones

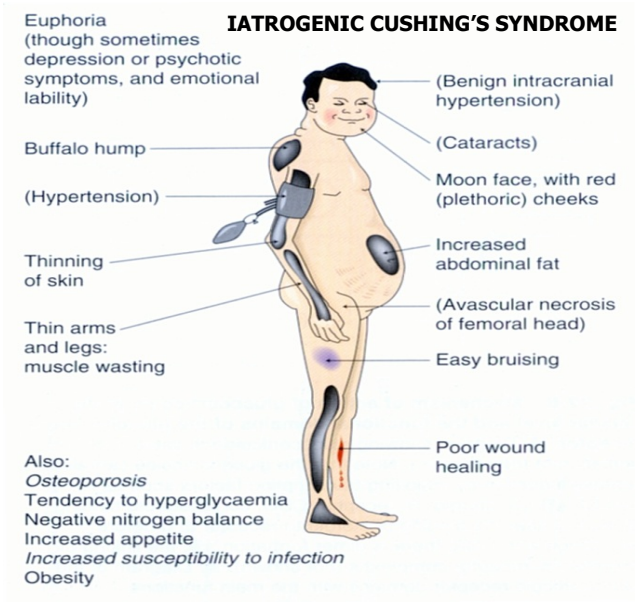
- Intravenous corticosteroids can be administered when patients are too dyspneic to swallow; if the patient is vomiting; or when patients require non-invasive ventilation or intubation
- oral administration is as effective as intravenous
- In status asthmaticus hydrocortisone is given intravenously, followed by **oral prednisolone**

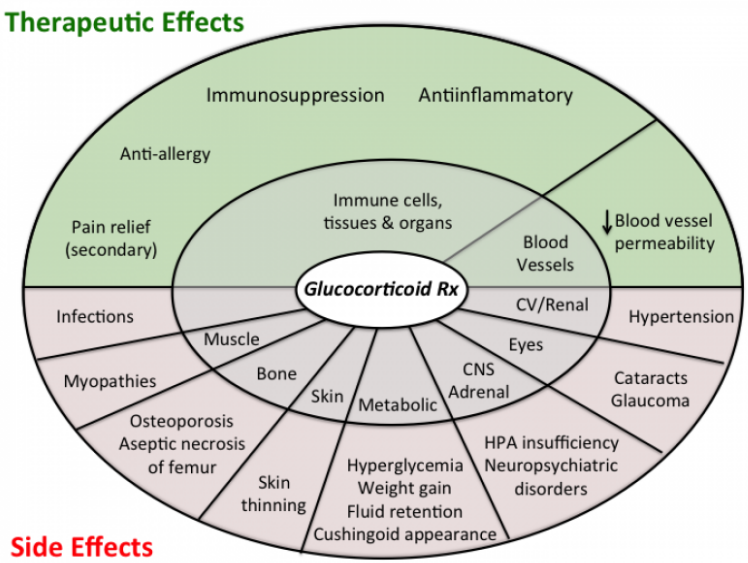
Inhaled GLUCOCORTICOIDS
Side effects

- Pharyngeal irritation
- Coughing
- Dry mouth
- Hoarseness
- **Oral fungal infections** (oral thrush, oropharyngeal candidiasis)
- **Systemic effects are rare because of the low doses used for inhalation therapy**

GLUCOCORTICOIDS
Side effects of prolonged use

- Treatment **with high-dose steroids** can cause hypertension, diabetes, GI bleeding and CNS disturbances
- **Long-term steroid** use produces a wide range of severe side effects: thinning of the skin (striae, bruising), osteoporosis, aseptic necrosis of the femoral head, ulceration, bleeding, diabetes with complications, CNS disturbances (psychosis), suppression of adrenal function, acne, Cushingoid appearance: moon face, buffalo hump, increased susceptibility to infection (immunosuppression)





GLUCOCORTICOIDS (CORTICOSTEROIDS)

INHALED STEROIDS ICS

- Beclomethasone
- **Budesonide**
- Ciclesonide
- Fluticasone
- Flunisolide
- Mometasone
- Triamcinolone

ORAL STEROIDS OCS

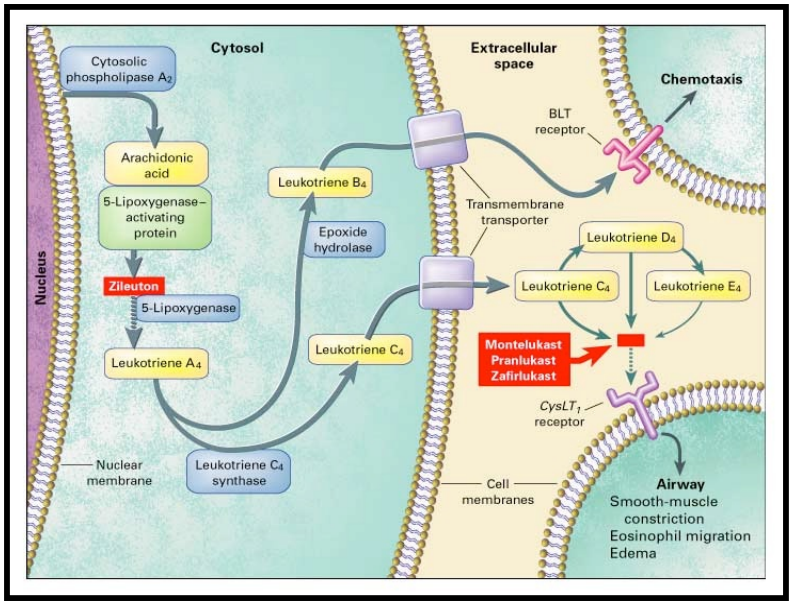
- Hydrocortisone
- **Prednisone**
- Prednisolone
- Dexamethasone
- Methylprednisolon

Leukotriene modifiers

- **Block the production or function of leukotrienes and subsequently prevent inflammation**
- Leukotrienes are potent broncho-constrictors, cause inflammation and mucus secretion
- LTC4 and LTD4 potent bronchoconstrictors (1000 x > histamine); produce mucosal edema and increase microvascular permeability
- LTB4 causes neutrophil chemotaxis/aggregation and the release of enzymes and inflammatory mediators

Leukotriene modifiers

- Antagonizes the effects of leukotrienes, which mediate the following: airway edema, smooth muscle constriction, altered cellular activity
- **5-lipooxygenase (5-LO) inhibitor:** Zileuton
- **leukotriene Cys LT1 receptor antagonists (LTRA): Zafirlukast, Montelukast**
- Advantage: PO administration



Leukotriene inhibitors
Clinical use

- Alternative, but not preferred for **mild persistent asthma**
- **Exercise induced asthma**
- **Aspirin-sensitive asthma**

- **Montelukast** >2 y.o, chewable tabs taken once a day in the evening
- **Zafirlukast** >7 y.o

Aspirin-induced hypersensitivity: asthma and angiodema

- Inhibition of cyclooxygenase → Build up of arachidonic acid → metabolised to leukotrienes → rhinitis, asthma and angiodema
- 5-10% of asthmatics are sensitive to aspirin
- Avoid all NSAIDs after a hypersensitivity reaction

BIOLOGICAL THERAPY for asthma

- **Biological therapy** is mostly indicated for patients with severe eosinophilic phenotype of asthma (anti-IL5/IL5R, anti-IL4R therapy) or for severe allergic asthma (IgE-dependent asthma, patients allergic to year-round allergens)
- Anti-IgE Monoclonal ANTIBODY: OMALIZUMAB
- Anti-interleukin 5 (IL-5) therapy: MEPOLIZUMAB, RESLIZUMAB
- Anti-interleukin 5 receptor (IL-5R) therapy: BENRALIZUMAB
- Anti-interleukin 4 receptor (IL-4R) therapy: DUPILUMAB

Anti-IgE Monoclonal ANTIBODY OMALIZUMAB

- a monoclonal antibody directed at FcεR1, the receptor for allergen-bound IgE on mast cells and basophils that mediates histamine release
- histamine release is blocked and surface FcεR1 receptors are down-regulated
- not first line, only works in severely atopic patients
- s.c injection **lessen asthma severity and reduce the corticosteroid requirement in patients with moderate to severe disease** (IgE-dependent asthma); >6 y.o

Anti-interleukin 5 (IL-5) therapy MEPOLIZUMAB

- **IL-5 is one of the most important cytokines in the development and activation of eosinophils, which are associated with inflammation in asthma**
- fully humanized monoclonal antibody that targets IL-5 and prevents binding to the IL-5 receptor on the surface of eosinophils
- indicated for the add-on maintenance treatment of patients >12 years with **severe asthma with an eosinophilic phenotype**; s.c injection
- is not indicated for the relief of acute bronchospasm or status asthmaticus
- decreases in corticosteroid doses
- side effects: rash, flushing, pruritus, headache, mialgia

Anti-interleukin 5 (IL-5) therapy RESLIZUMAB

- IL-5 antagonist (immunoglobulin G4-kappa)
- binds to the alpha chain of the IL-5 receptor on the eosinophil surface to **inhibit the proliferation of eosinophils**
- indicated for patients 18 years of age and older as an add-on maintenance treatment of **severe asthma with an eosinophilic phenotype**, is not indicated for the relief of acute bronchospasm or status asthmaticus; i.v injection

Anti-interleukin 5 receptor (IL-5R) therapy BENRALIZUMAB

- humanised anti-interleukin-5 receptor α monoclonal antibody
- action on the IL-5 receptor in basophils and eosinophils produces the apoptosis and its significant reduction in the blood
- indicated as a maintenance treatment of patients 12 years or older with **severe asthma and an eosinophilic phenotype**; s.c injection

Anti-interleukin 4 receptor (IL-4R) therapy DUPILUMAB

- **Interleukin-4 (IL-4) mediates important pro-inflammatory functions in asthma including induction of the IgE isotype switch, expression of vascular cell adhesion molecule-1 (VCAM-1), promotion of eosinophil transmigration across endothelium, mucus secretion, and differentiation of T helper type 2 lymphocytes leading to cytokine release**
- anti-interleukin-4 receptor α monoclonal antibody, binds to the alpha subunit of the interleukin-4 receptor (IL-4Rα), making it a receptor antagonist
- indicated for patients with severe **eosinophilic phenotype of asthma** and **steroid-dependent asthma**; s.c injection; >12 y.o

Biological drugs used in asthma

Drug	Mechanism of action	Route of administration	Clinical use
Omalizumab	binding IgE	sc	patients allergic to year-round allergens
Mepolizumab **Reslizumab**	binding IL-5	mepolizumab - sc reslizumab - iv	eosinophilic phenotype of asthma
Benralizumab	binding IL-5 receptor	sc	eosinophilic phenotype of asthma
Dupilumab	binging IL-4 receptor	sc	eosinophilic phenotype of asthma steroid-dependent asthma

Asthma Classification

STEP 1: **MILD INTERMITTENT**	symptoms less than twice a month
STEP 2: **MILD PERSISTENT**	symptoms twice a month or more, but less than daily
STEP 3: **MODERATE PERSISTENT**	symptoms most days, or waking with asthma once a week or more
STEP 4: **SEVERE PERSISTENT**	symptoms most days, or waking with asthma once a week or more, or low lung function
STEP 5: **SEVERELY UNCONTROLLED**	symptoms most days, frequent asthma exacerbations

RECOMMENDED TREATMENT REGIMENS OF ASTHMA **GINA 2023**

Therapy intensity levels						
		STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
LONG-TERM control medications CONTROLLER	PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As needed low dose ICS/FORM	Low dose ICS or as needed low dose ICS/FORM	Low dose maintenance ICS/FORM	Medium dose maintenance ICS/FORM	High dose ICS/ LABA/LAMA Refer for phenotypic assessment, add-on therapy: tiotropium, anti-IgE, anti-IL5/ IL5R, anti-IL4R
	Other controller options	As needed low dose ICS + SABA	LTRA or low dose ICS + SABA	Low dose ICS/LABA Medium ICS or low dose ICS+LTRA	Medium or high dose ICS + LABA tiotropium or LTRA	Low dose OCS but consider side-effects prednisone
SHORT-TERM control medications RELIEVER	PREFERRED RELIEVER	As needed low dose ICS/FORMOTEROL budesonide/formoterol				
	Other reliever option	As needed SABA or as needed ICS/SABA				

Severe asthma exacerbation
Emergency treatment

- Medical emergency requiring hospitalisation
- **Oxygen inhalation:** to achieve arterial oxygen saturation of 93–95% (94–98% for children 6–11 years), oxygen should be administered by nasal cannulae or mask
- **Inhaled short-acting beta2-agonists:** SABA therapy should be administered frequently for patients presenting with acute asthma. The most efficient delivery is by pMDI with a space. Current evidence does not support the routine use of intravenous beta2-agonists
- **Epinephrine** (for anaphylaxis): itramuscular epinephrine is indicated in addition to standard therapy for acute asthma associated with anaphylaxis and angioedema. It is not routinely indicated for other asthma exacerbations.

Severe asthma exacerbation
Emergency treatment

- **Systemic corticosteroids:** speed resolution of exacerbations and prevent relapse; particularly important in the emergency department if:
- initial SABA treatment fails to achieve lasting improvement in symptoms
- the exacerbation developed while the patient was taking OCS
- the patient has a history of previous exacerbations requiring OCS
- Route of delivery: **oral administration is as effective as intravenous**
- daily doses of OCS equivalent to 50 mg **prednisolone** as a single morning dose, or 200 mg **hydrocortisone** in divided doses (children: 1–2 mg/kg up to a maximum of 40 mg/day)

Severe asthma exacerbation
Emergency treatment

- **Inhaled corticosteroids:** high dose ICS given within the first hour after presentation reduces the need for hospitalization in patients not receiving systemic corticosteroids
- **Other treatments:**
- **ipratropium bromide** - in the ED treatment with both SABA and ipratropium
- **aminophylline and theophylline** - intravenous aminophylline and theophylline should not be used in the management of asthma exacerbations (potentially fatal side-effects, particularly in patients already treated with sustained-release theophylline)

SUMMARY OF IMPORTANT POINTS

- Drugs used in the management of asthma are classified as **antiinflammatory** agents or **bronchodilators**, but some drugs exhibit both antiinflammatory and bronchodilating action.
- **Corticosteroids, the most efficacious antiinflammatory drugs**, are usually given by inhalation on a long-term basis to prevent asthmatic attacks. Orally (or parenterally administered) steroids are used for the management of chronic severe asthma or acute exacerbations of asthma.
- **Leukotriene inhibitors have antiinflammatory and bronchodilating activity** and offer convenient oral therapy for the prevention of asthmatic attacks. Montelukast and zafirlukast are leukotriene receptor antagonists, and zileuton is a leukotriene synthesis inhibitor.

- **Short-acting β2-adrenoceptor agonists are the most efficacious bronchodilators for the treatment of acute bronchospasm** (salbutamol, fenoterol). **Long-acting β2-agonists** (salmeterol and formoterol) are **used to prevent bronchospasm**. Indacaterol, wilanterol are an ultralong-acting β2-agonist recently approved for once-daily administration. **Preferred reliever: ICS/FORMOTEROL (GINA 2023)**
- **Ipratropium and tiotropium are muscarinic receptor antagonists that are primarily used to treat COPD.**
- **Theophylline has antiinflammatory and bronchodilating activity and is useful for the treatment of asthma and COPD**.
- Theophylline levels should be monitored to ensure efficacy and prevent toxicity. Adverse effects include gastrointestinal, central nervous system, and cardiac toxicity.

- **Biological therapy** is mostly indicated for patients with severe eosinophilic phenotype of asthma (anti-IL5/IL5R, anti-IL4R therapy) or for severe allergic asthma (IgE-dependent asthma, patients allergic to year-round allergens)
- **Antitussives are used to suppress dry, nonproductive coughing**. Dextromethorphan is available without a prescription, whereas codeine and hydrocodone are contained in many prescription cough preparations.
- **Butamirate** is a safe nonopioid centrally acting antitussive, used in children from 8 months of age.

- **Expectorant** drugs (**mucolytics and mucokinetics**) don't block cough reflex. By loosening and thinning sputum and bronchial secretion, the tendency to cough is indirectly diminished. Used for the relief productive cough associated with common cold, bronchitis, laryngitis, pharyngitis, pertussis.
- **Mucolytics** (ACC, erdosteine, carbocisteine, ambroxol) facilitate removal of viscous and inspissated pulmonary secretion by rupturing disulfide bond of the mucus.
- ACC (IV) is used in paracetamol overdose.
- Mesna (IV) is an adjuvant used in cancer chemotherapy involving cyclophosphamide (prevent urinary bladder toxicity).