Treatment of Bronchial Asthma

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Factors in the Treatment Strategy

- **Asthma is a *chronic* condition.**
- **The goal of therapy is *normal function.***
- **The Condition is *heterogeneous* in terms of:**
  - **Cause or trigger mechanism.**
  - **Extent of bronchoconstriction *and***
  - **Degree of inflammation.**
- **The course is *unpredictable.***
- **Therapy must be *individualized.***

Risk of Not Treating Asthma

- **Poor or no control of the patient's asthma.**
- **Accelerated decline in the function of the patient's lungs as measured by PFT's.**
- **Increased number of attacks of asthma.**
- **Poorer response to therapy if started late.**
- **Increased mortality from asthma.**

Goals of Therapy in Asthma

- **Minimal symptoms even during sleep.**
- **No, or infrequent, acute episodes.**
- **No emergency visits or missed days in school or work.**
- **Rare need for beta-agonist inhaler therapy.**
- **No limitation of activities – even sports.**
- **Peak flow rate variability less than 20%.**
- **FEV_1 consistently >80% of predicted range.**
- **No or minimal adverse effects from drugs.**

Pathogenesis

- **Early Asthmatic Response:**

Allergens provoke IgE production.

The tendency to produce IgE is genetically determined.

Re-exposure to the allergen causes antigen- antibody interaction on the surface of the mast cells leading to:

Release of stored mediators.

Synthesis of other mediators.

Also, activation of neural pathways

All will result in bronchoconstriction

Prevented by bronchodilators.

Pathogenesis

- **Late Asthmatic Response:**

4-5 hours later.

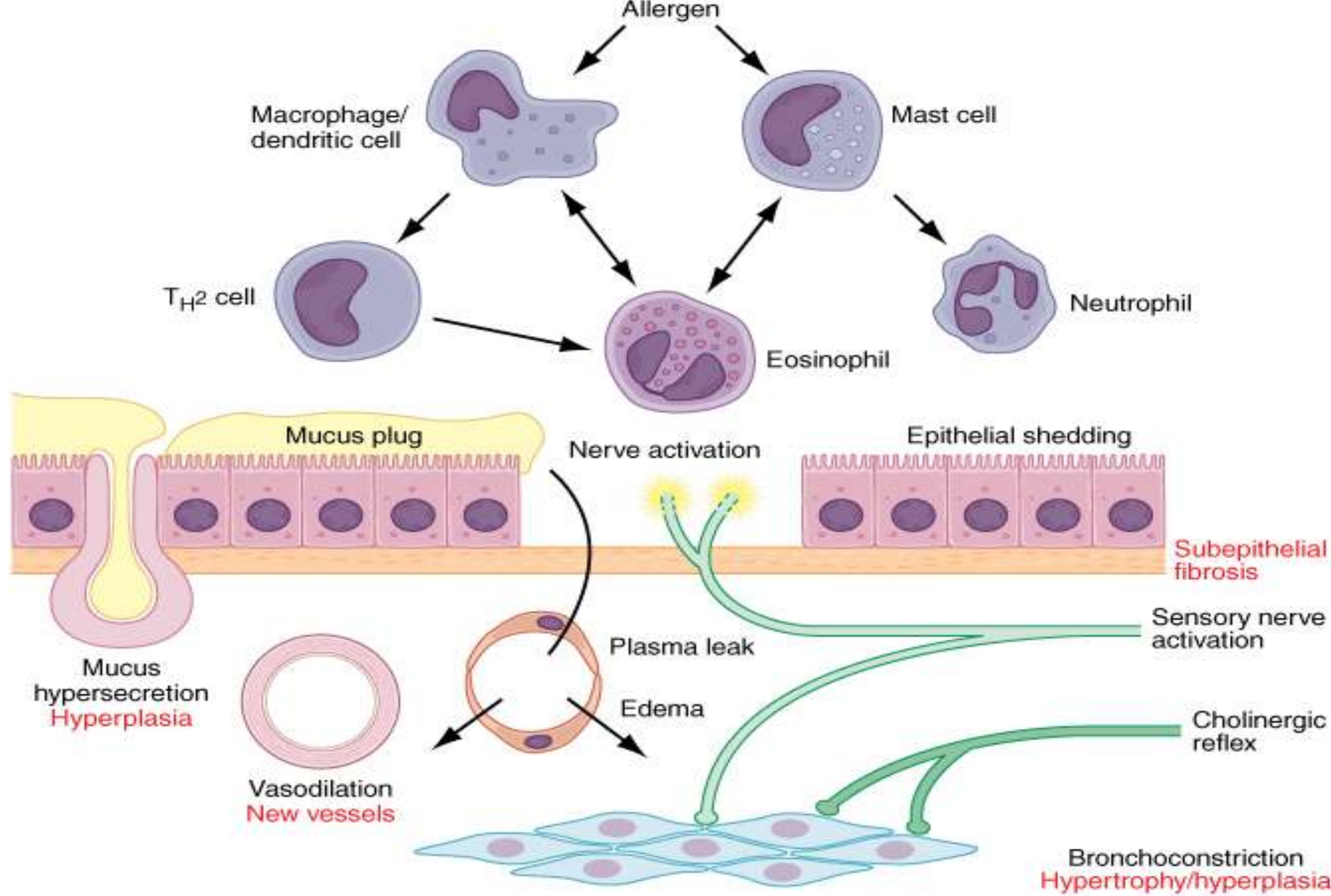
More sustained phase of bronchoconstriction.

Influx of inflammatory cells and an increase in bronchial responsiveness.

The mediators here are cytokines produced by TH2 lymphocytes, especially interleukins 5, 9, and 13.

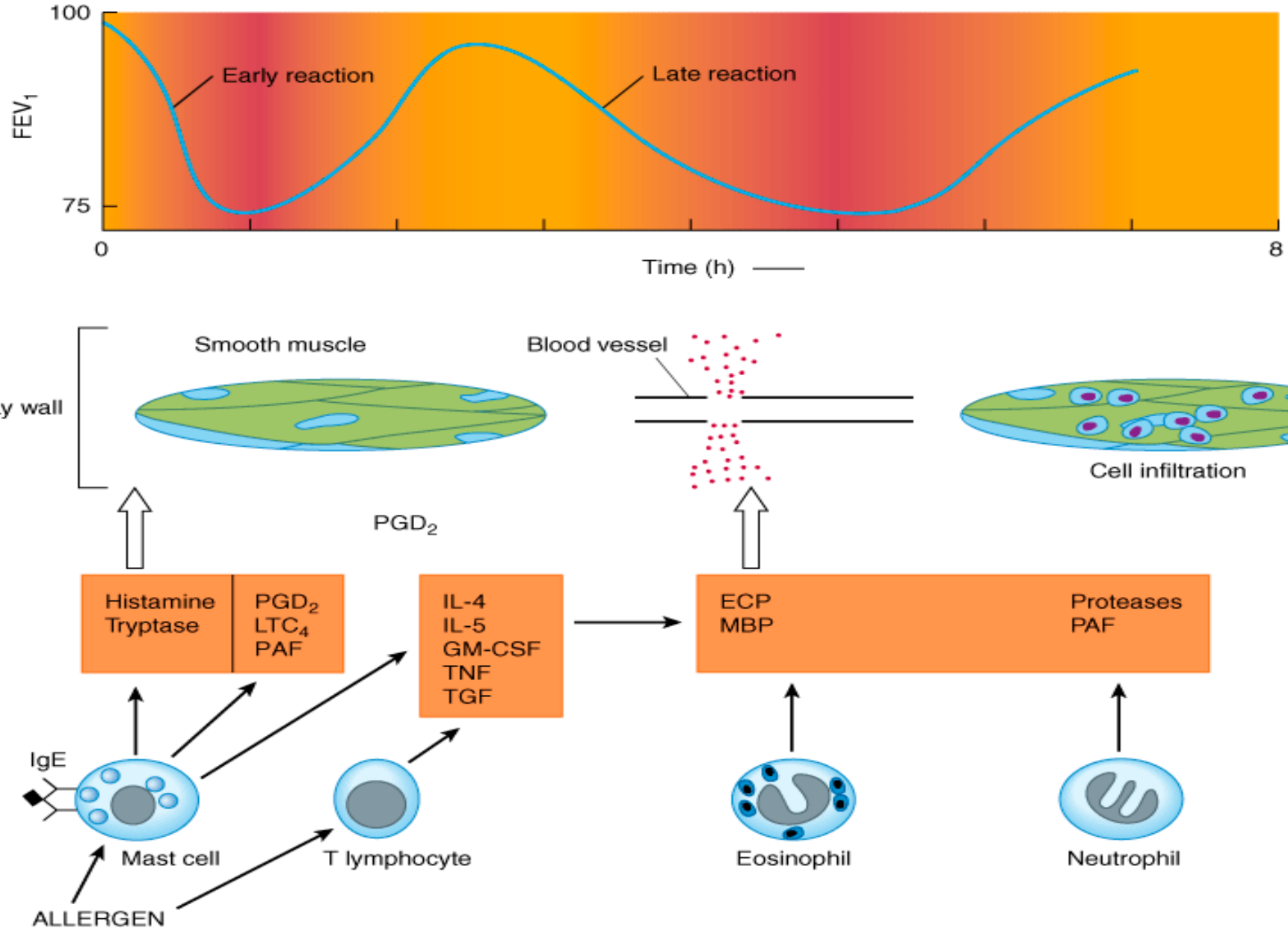
These will stimulate IgE production by B lymphocytes, and directly stimulate mucus production.

Prevented by corticosteroids.



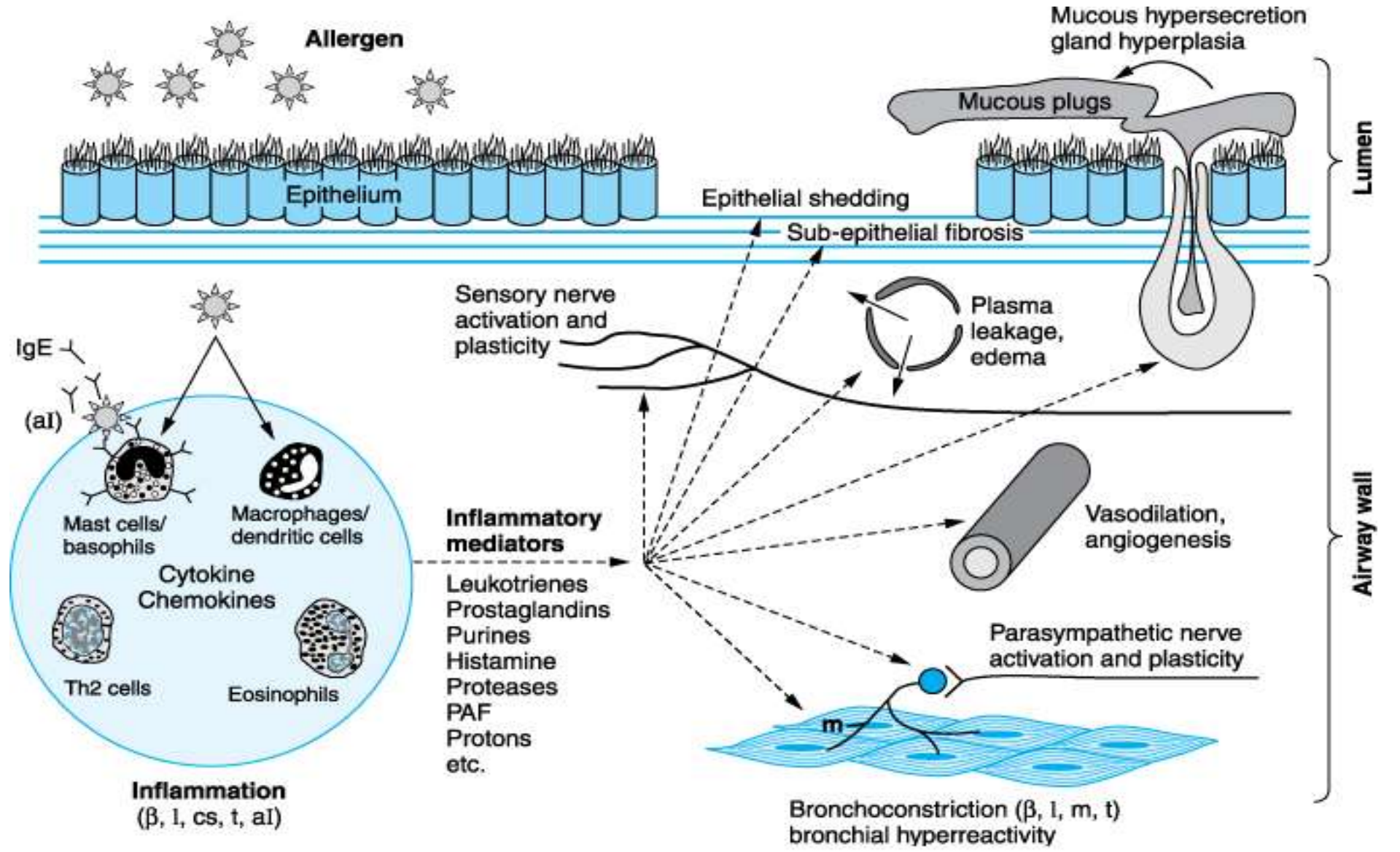
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Immunopathogenesis of asthma.

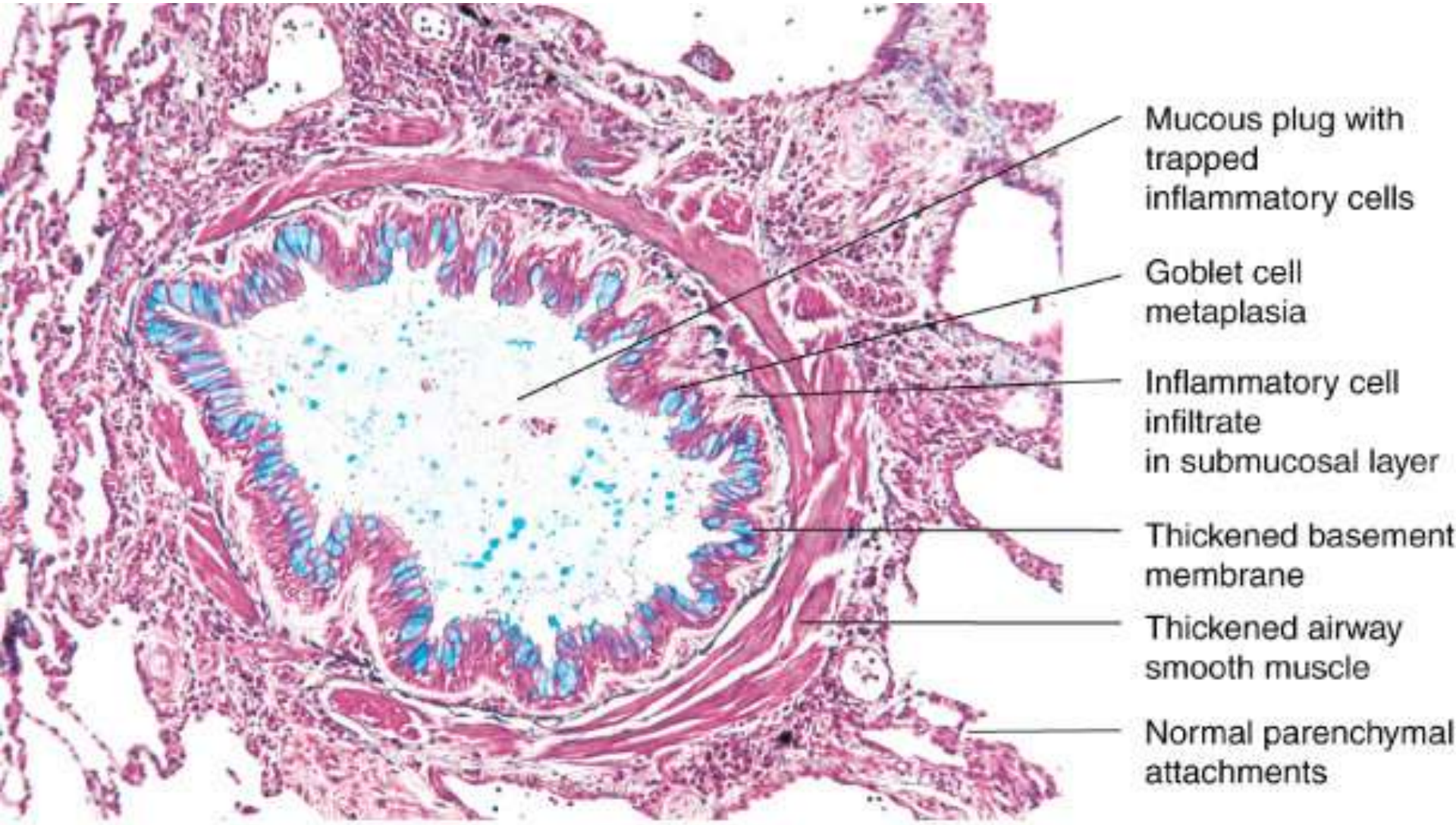


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Simplified view of allergic inflammation in the airways.



Histopathology of a small airway in fatal asthma



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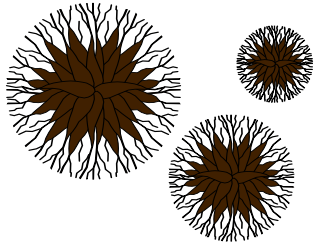
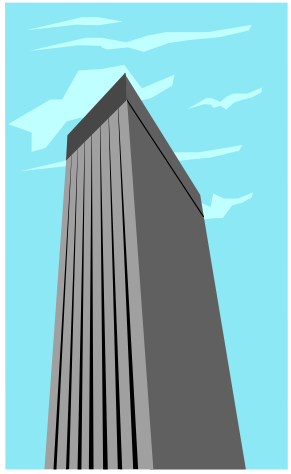
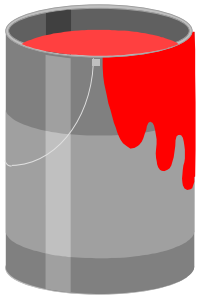
Asthma Triggers

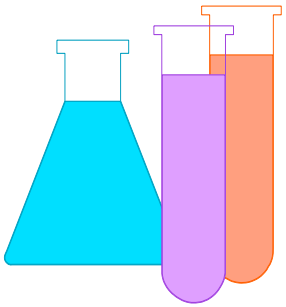
- **Exercise / cold air**
- **Cigarette smoke**
- **Stress / anxiety situations**
- **Animal dander's (cats, dogs etc..)**
- **Allergens (grass, trees, molds, cockroach)**
- **Pollutants (sulfur dioxide, ozone, etc…)**
- **Fumes/toxic substances**
- **Medications (ASA, NSAID's, others)**
    -

Asthma Triggers









Diagnosis of Asthma - Subjective

- ✓ **Cough - usually in spasms and to the point of vomiting - nighttime worse than daytime.**
- ✓ **Cough may follow exposure to cold air, exercise, a URI (common cold), or allergen**
- ✓ **Dyspnea > cough or wheezing > sputum.**
- ✓ **Past history of bronchiolitis as a child**
- ✓ **Family history of asthma is common**

Diagnosis of Asthma - Objective

- Diminished Peak Expiratory Flow Rate (PEFR)
- Reduced FEV_1 and FEV_1/FVC ratio
- Reduced mean and Forced Expiratory Flow Rate (FEFR)
- Reversibility with Bronchodilators
- Heightened response to Methacholine Test.
- Increase in expired Nitric Oxide
- Increase in Inflammatory Mediators and their metabolic products in body fluids

Myths and Misconceptions

- ✓ **Patient and physician "Steroid-o-phobia".**
- ✓ **Asthma is an emotional illness.**
- ✓ **Asthma is an acute disease.**
- ✓ **Asthma medications are addictive.**
- ✓ **Asthma medications become ineffective if they are used regularly.**
- ✓ **Asthma is not a fatal illness / It does not kill.**

Survey of the changing therapy of asthma by decade

1960's

Aminophylline, Epinephrine, Ephedrine

1970's

Beta-agonists, Theophyllines, Beclomethasone, Cromolyn, Ipratropium

Survey of the changing therapy of asthma by decade

1980's

Beta-agonists, Inhaled Corticosteroids, Cromolyn, Ipratropium

1990's

Inhaled Corticosteroids, Beta-agonists, Theophylline, Leukotriene Inhibitors

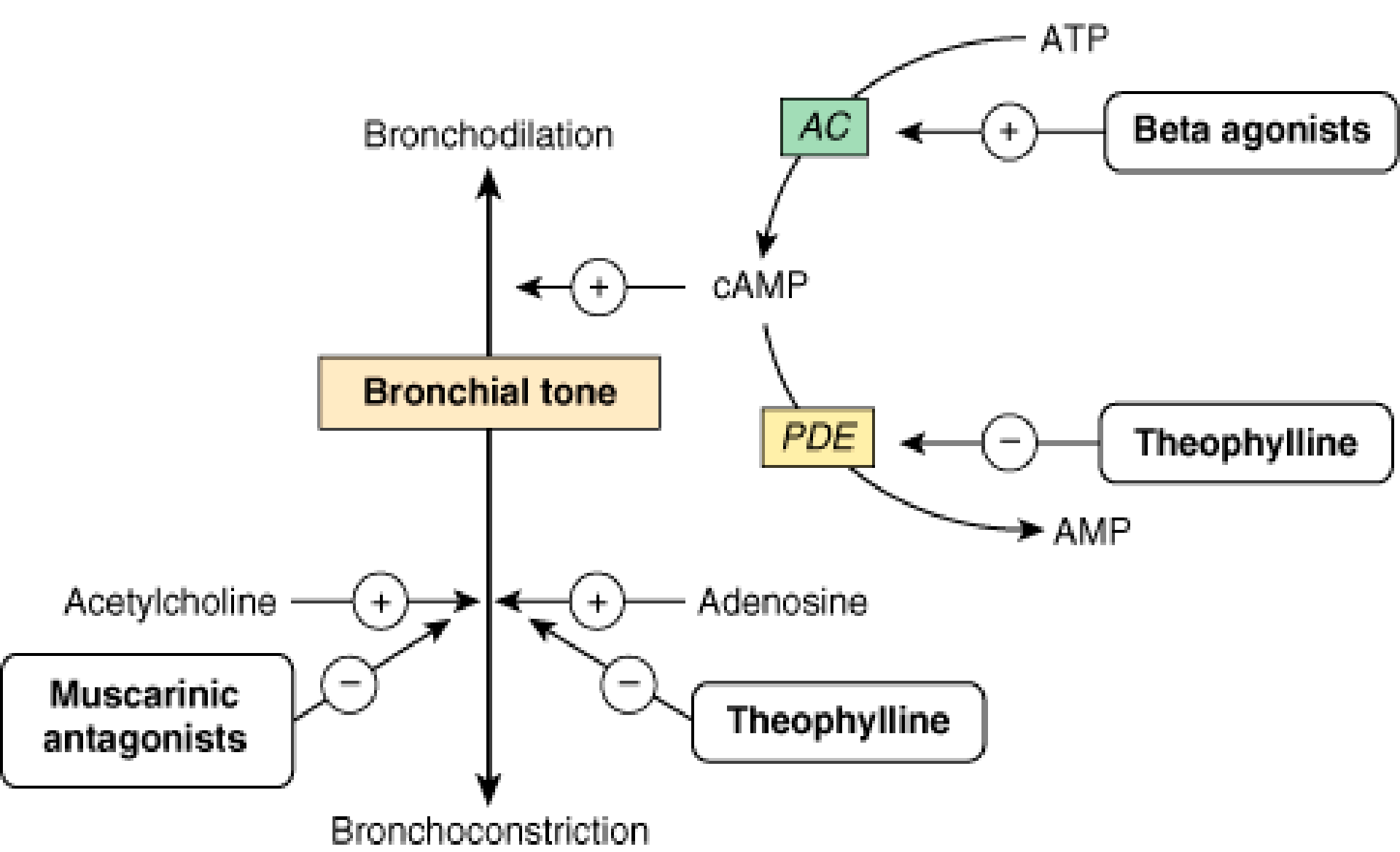
Survey of the changing therapy of asthma by decade

2000's

Corticosteroids + LABA, LTRAs, Theophylline, Cromolyn, Ipratropium, Tiotropium

2010's

Prevention including gene therapy.



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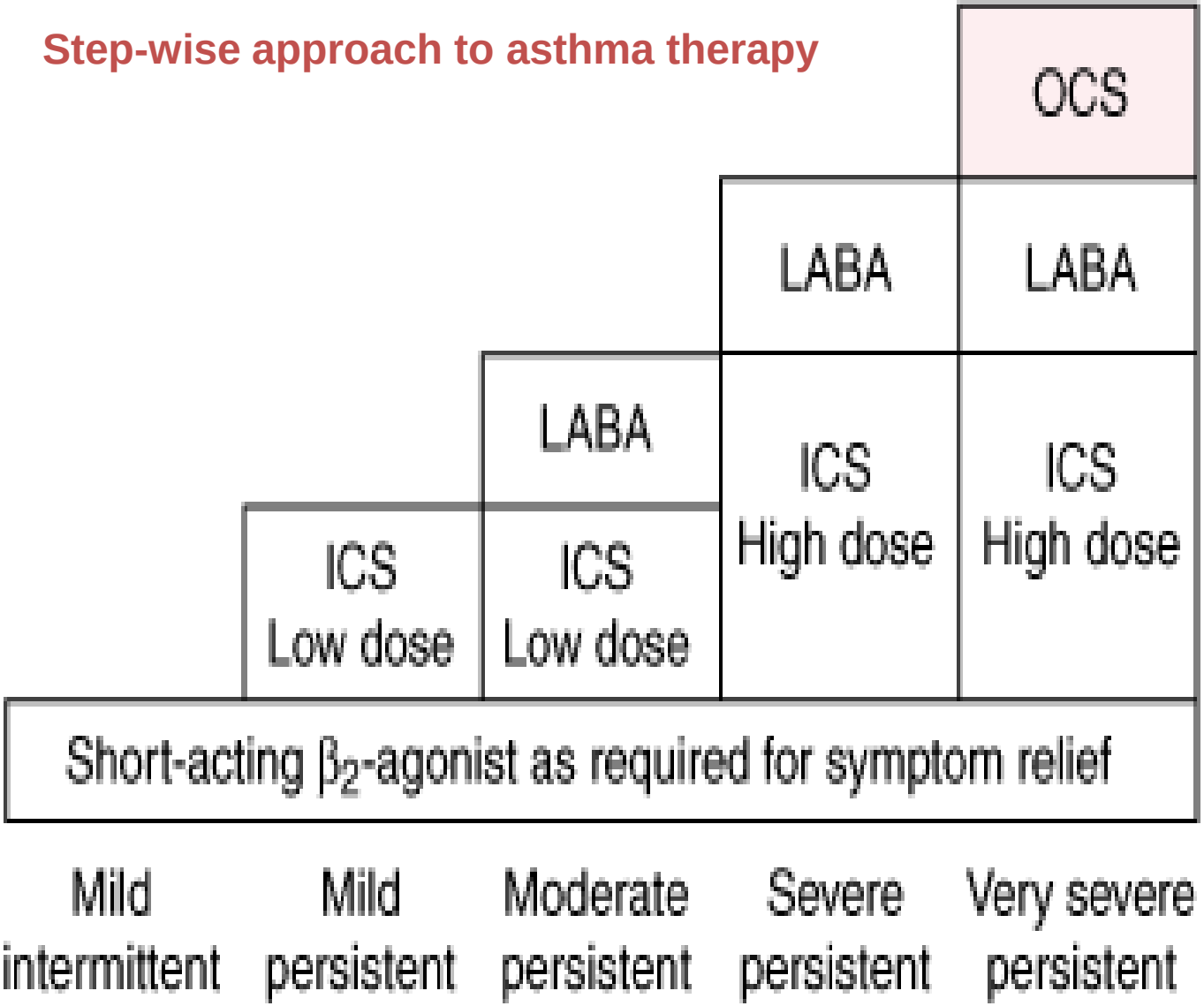
Step-wise approach to asthma therapy



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

General Therapy of Asthma

- **Oxygen.**
- **Hydration: Oral or Intravenous.**
- **Expectorants.**
- **Antimicrobials.**

Relievers / Controllers

- **Quick relief medications:**
  - Inhaled Short acting Beta-2 Agonists
  - Inhaled Anticholinergics
  - Systemic Corticosteroids
- **Long-term control medications:**
  - Topical (inhaled) Corticosteroids
  - Inhaled Cromolyn Na and Nedocromil
  - Oral Methylxanthines (Theophyllines)
  - Inhaled Long-acting Beta-2 Agonists (LABA)
  - Oral Leukotriene modifiers (LTRA)

Beta 2-Adrenergic Agonists

- **Pharmacological Actions:**

Bronchodilation.

Tremor.

Tachycardia.

Fall in blood pressure.

Slight fall in plasma potassium.

Beta 2-Adrenergic Agonists

- ✓ Medication of choice for acute exacerbations
  - ✓ Actively relax airway smooth muscle.
  - ✓ Inhibit release of mediators.
  - ✓ Enhance muco-cilliary activity.
  - ✓ Decrease vascular permeability.
  - ✓ Inhibit eosinophil activation.

Beta 2-Adrenergic Agonists

- **Molecular Actions:**

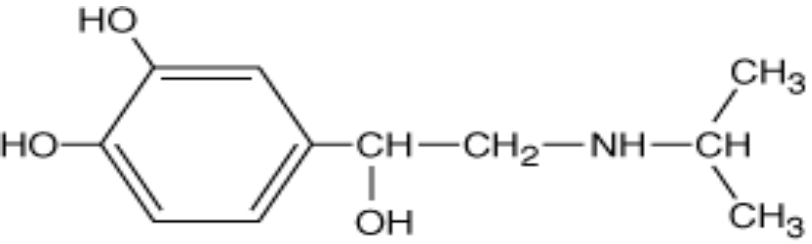
Activate adenylate cyclase leading to increased cAMP.

Activate protein kinase A.

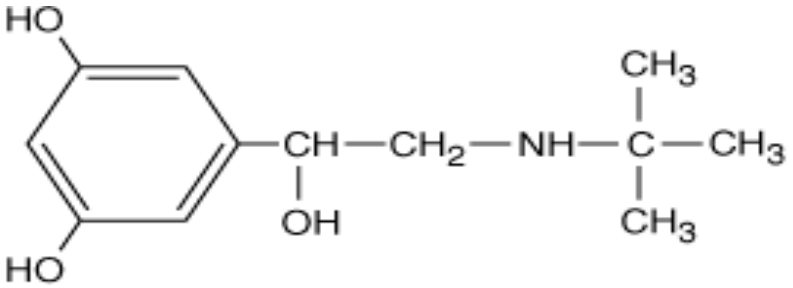
Phosphorylate kinases.

All lead to decreased cytosolic Ca++.

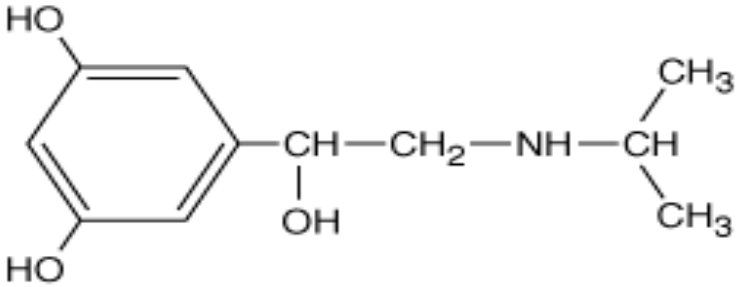
Beta2-Selective Drugs



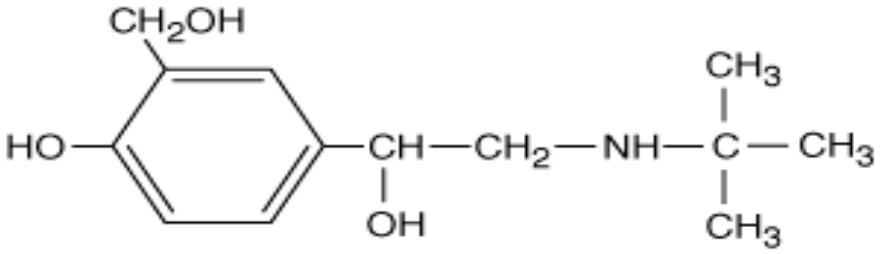
Isoproterenol



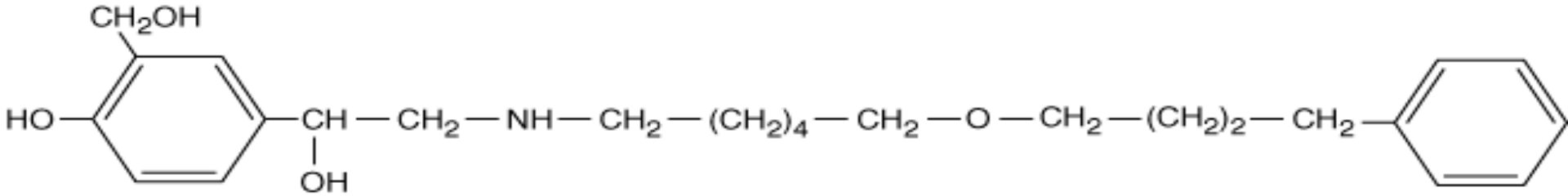
Terbutaline



Metaproterenol



Albuterol (salbutamol)



Salmeterol

Beta 2-Adrenergic Agonists

- **Epinephrine:**

Bovine adrenal gland.

Not selective,also stimulates α, β1 receptors.

Not effective orally.

Inhalation.

Subcutaneous.

Beta 2-Adrenergic Agonists

- **Isopreterenol:**

Stimulates β1 and β2 receptors.

First (1960s) convenient, pocket- sized multidose inhalers.

Considerable tachycardia and pounding.

Short Acting Beta 2-Adrenergic Agonists

- **Albuterol.**
- **Terbutaline.**
- **Pirbuterol.**
- **Metaproterenol.**
- **Isoetharine.**

Beta 2 selective

Rapid onset: 3-5 minutes.

Maximal effect: 30-60 minutes.

Duration: 4-6 hours.

Long Acting Beta 2-Adrenergic Agonists(LABA)

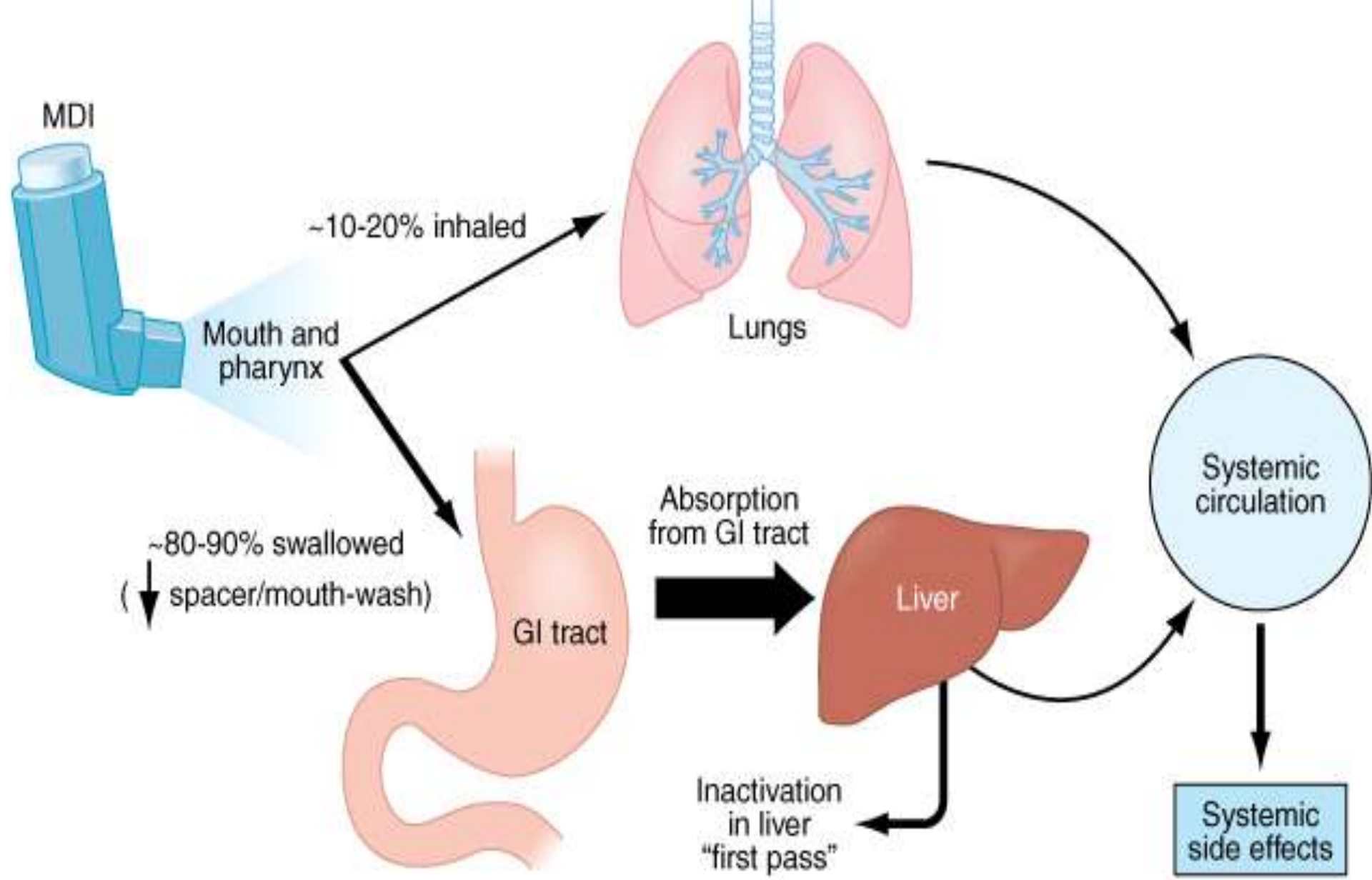
- **Salmeterol.**
- **Formeterol.**

Duration of action: 12 hrs.

Suppress nighttime attacks.

Controllors with steroids.

No tachyphylaxis.



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Problems of Metered Dose Inhalers(MDI)

- **Cap not removed prior to use in some patients**
- **Timing of canister actuation to inspiration is critical - only first air gets into the right place.**
- **Inspiration too rapid - should take 4 - 5 seconds**
- **Nasal inspiration contains no medication.**

➢ **To use MDI's correctly requires instructions and training.**

Beta 2-Adrenergic Agonists

- ✓ Medications of choice for acute exacerbations
  - ✓ Actively relax airway smooth muscle
  - ✓ Enhance muco-cilliary clearance
  - ✓ Decrease vascular permeability

However, short-acting formulations are to be used on a p.r.n. basis only - regular use is associated with diminished control.

Beta 2-Adrenergic Agonists

- **<u>TOXICITY:</u>**
- **Nervousness, Anxiety, Tremor**
- **Due to vasodilation, may increase perfusion of poorly ventilated lung units and might transiently decrease PaO2.**
- **Tachyphylaxis.**
- **Increased mortality due to cardiac toxicity.**

Pharmacogenetics of Beta 2-Adrenergic Agonists

Patients homozygous for glycine at the B-16 locus of the β receptor improved with regular use of albuterol or salmeterol.

Patients homozygous for arginine at the B-16 locus of the β receptor(found in 16% of Caucasians and more frequently in blacks) deteriorated with regular use of albuterol or salmeterol

Methylxanthines

- **Theophylline.**
- **Aminophylline.**

Were the mainstay treatment.

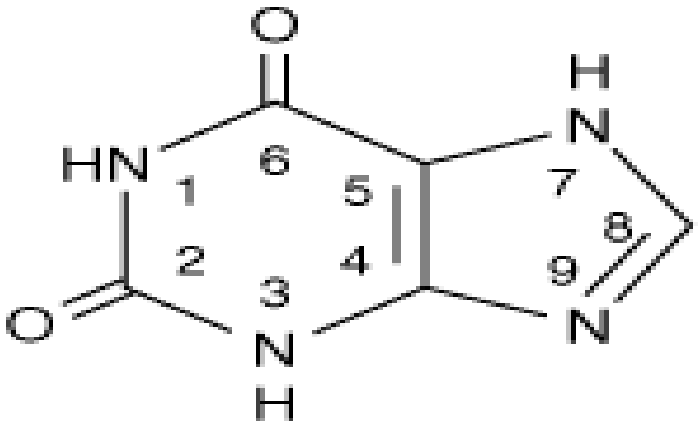
Oral and Intravenous.

CNS stimulants

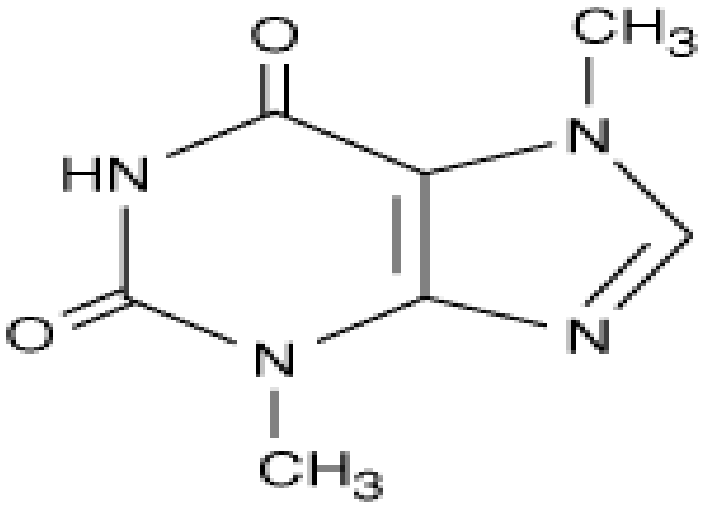
Cardiovascular stimulants; arrhythmias.

Nausea, GIT irritation, diarrhea.

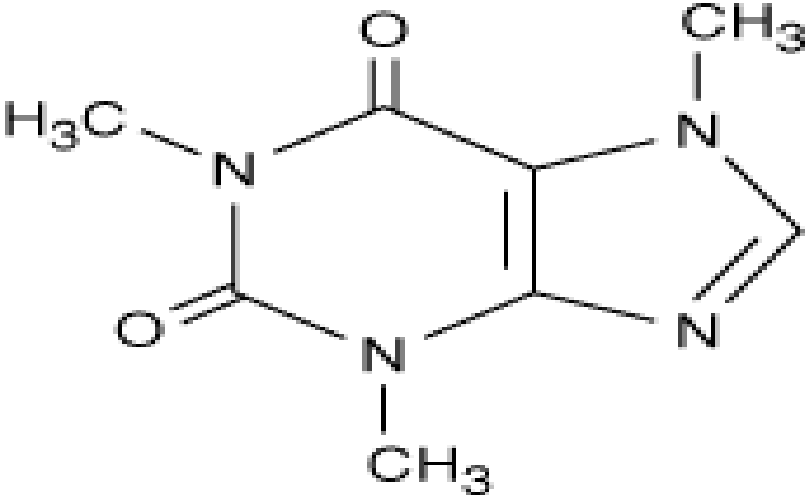
METHYLXANTHINE DRUGS



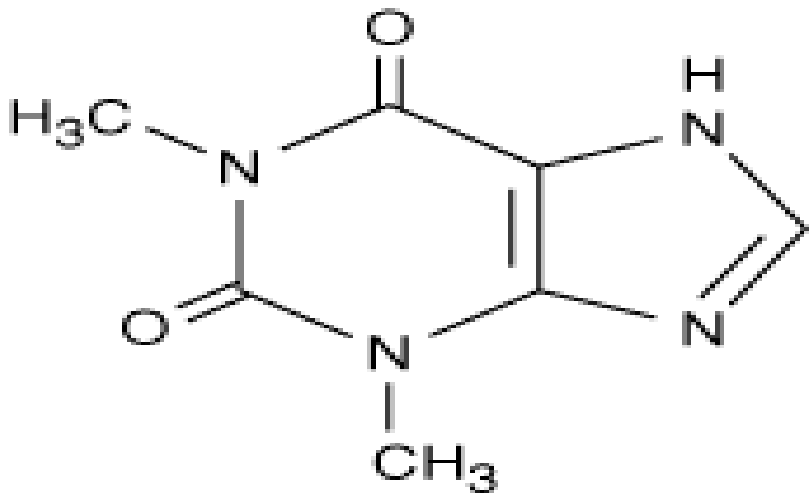
Xanthine



Theobromine



Caffeine



Theophylline

Mechanism of Action of Methylxanthines

- **Phosphodiesterase inhibition.**
- **Adenosine receptor stimulation.**
- **Antiinflammatory activity.**

Problems with Methylxanthines

Optimal dosing is very difficult.

Wide inter-individual variation in the rate of hepatic metabolism.

Half life: 3-16 hours.

Food and drug interactions (erythromycins and ciprofloxacin).

Blood assay is a routine.

Theophylline Returns

- **Resurgence of an old friend:**

Use of low dose theophylline, with mean plasma level of 36.6 µmol/ml (6.7 µg/ml), significantly inhibits the Late Asthmatic Reaction (LAR) and airway inflammatory infiltration.

Anticholinergic Agents

- **<u>Atropine:</u>**

Can be inhaled, but; can cause systemic side effects.

Impairs mucociliary clearance leading to impaired clearance of airway secretions.

Anticholinergic Agents

- **Ipratropium Bromide Inhaler:**

Poorly absorbed from respiratory mucosa.

Does not impair clearance of airway secretions.

Causes minimal cardiac or central effects.

Anticholinergic Agents

- **Ipratropium Bromide Inhaler:**
- **Metered dose inhaler and as a solution for nebulization.**
- **Mainly for COPD, not for asthma, because of slow onset (10-15 minutes) and low potency.**
- **Might be very useful in special conditions(beta blocker- induced asthma, resistant attacks, cardiac patients)**

Anti-inflammatory Agents and Alternative Therapy

- **Coricosteroids.**
- **Inhibitors of Mast Cell Degranulation.**
- **Leukotriene Pathway Modifiers.**
- **Immunomodulatory Agents.**

Corticosteroids(1950s)

- Inhibit the synthesis and release of many chemical mediators (histamine, PGs and cytokines).
- Suppress the inflammatory cell influx and process.
- Relax bronchial smooth muscle.
- Enhance beta-adrenergic responsiveness (upregulate β receptors).
- Increase synthesis of adrenergic mediators.
- Decrease quantity and viscosity of secretions.
- Inhibit IgE synthesis.
- Decrease microvascular permeability.

Corticosteroids

Highly lipophilic, enter the cytosole.

- **Bind to cytosolic receptors.**
- **The drug-receptor complex enters the nucleus.**
- **Influences transcription of target genes.**
- **Decrease transcription of genes coding for pro inflammatory cytokines.**
- **Take several hours to days to work.**

Corticosteroids

Short term systemic use in severe refractory attacks.

Long term use for ”Steroid Dependant” asthma.

Corticosteroids

- **Systemic Use:**

  Oral or injectable

  (Cortisone, Prednisolone, Dexamethasone)

- **Inhalation:**

Aerosol treatment is the most effective way to avoid the systemic adverse effects

(Beclomethasone,Triamcinolone, Flunisolide, Budesonide, Fluticasone).

Corticosteroids

- **Local Side Effects:**

Hoarsness of voice (dysphonia), sore throat and cough.

Candida infection.

- **Systemic Side Effects:**

Osteoporosis, cataract, glaucoma, growth retardation, adrenal suppression, CNS effects and behavioral disturbances, increased susceptibility to infections, and teratogenicity.

Inhibitors of Mast Cell Degranulation

- **Cromolyn Na and Nedocromil Na:**

Inhibit the release of inflammatory mediators from mast cells (*Mast Cell Stabilizers*).

Prophylactic for mild to moderate asthma.

Regular use (4 times daily).

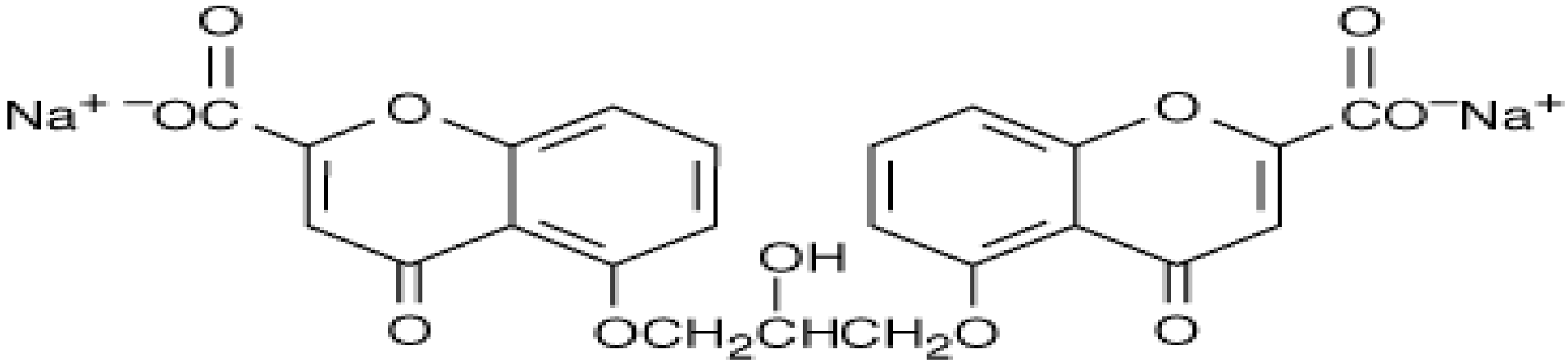
Not for acute asthma.

Phosphorylates a cell membrane protein, so, mediator release is inhibited despite antigen-IgE interaction.

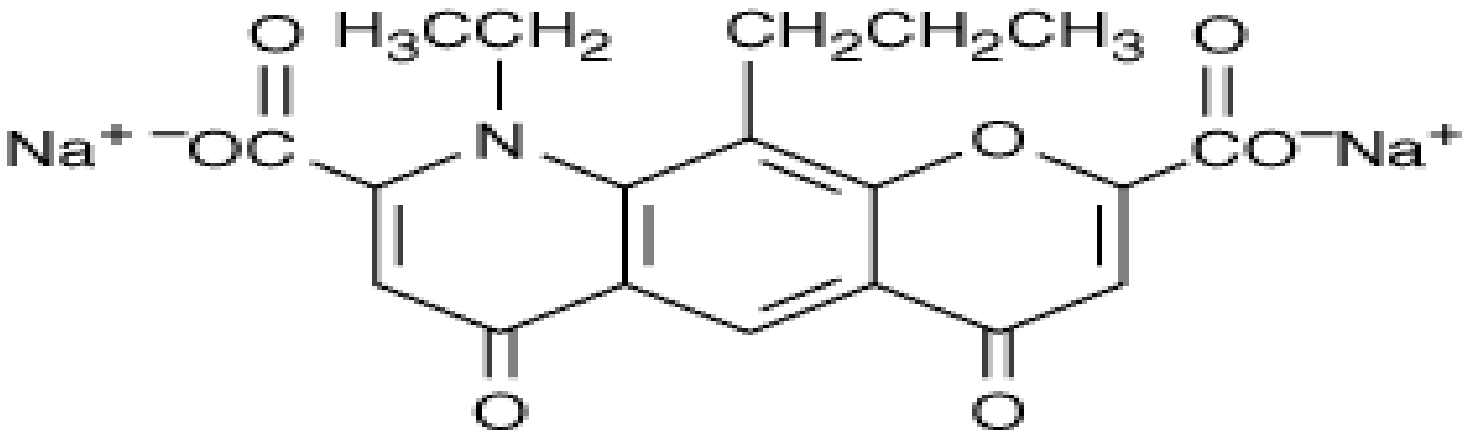
Might decrease Ca++.

Might decrease neural pathways, plasma exudation and inflammation in general.

Complete absence of side effects.



Cromolyn sodium



Nedocromil sodium

Leukotrienes

- Synthesized by mast cells and eosinophils.
- They are 1000-fold more potent than histamine in stimulating airway smooth muscle constriction.
- They also promote microvascular leakage, mucus secretion and eosinophil chemotaxis.
- Pathway augmented by COX inhibitors (i.e. NSAIDs)

Leukotriene Pathway Modifiers

- **3-5% of adults with asthma, have “aspirin sensitivity’.**
- **This reaction is not an allergic response, can be induced by many different chemicals (tetrazine, FDC Color #5), and does not involve IgE antibody response.**
- **Patients produce high levels of cysteinyl leukotrienes in response to COX inhibitors, probably by shunting of arachidonic acid into leukotriene pathway.**
- **Abnormality of the promotor region of the gene for LTC4 synthase, leading to overexpression of the enzyme leading to increased conversion of LTA4 to LTC4.**

Leukotriene Pathway Modifiers

- **Inhibitors of 5-Lipoxygenase enzyme:**

Zileuton: for acute and chronic treatment, 4 times daily, hepatotoxic.

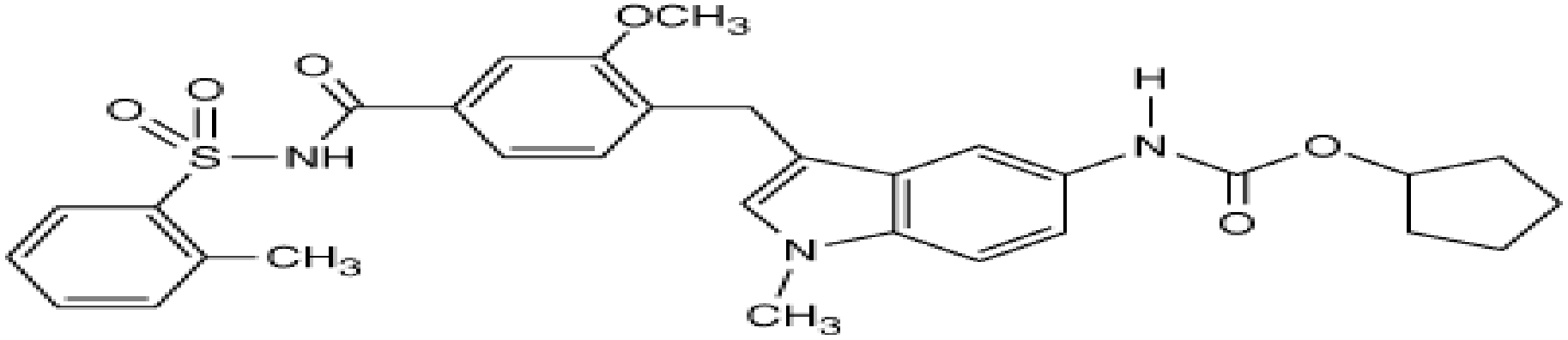
- **Antagonists of Cysteinyl Leukotriene Receptors:**

Montelukast.

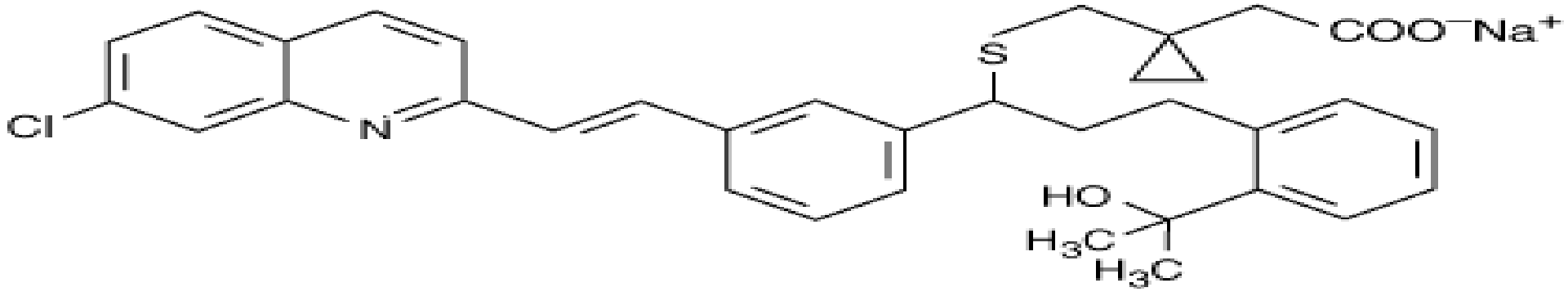
Zafirlukast.

Some patients improve, others do not (Churg-Strauss Syndrome.

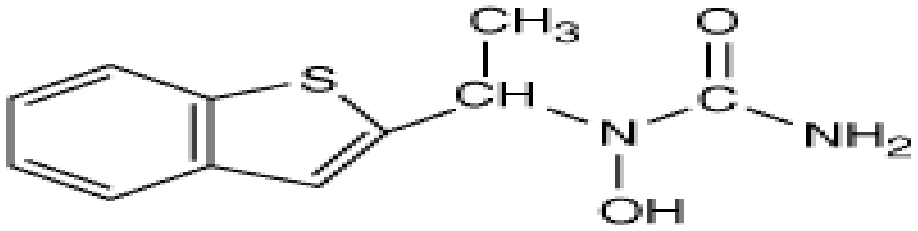
Leukotriene Pathway Inhibitors



Zafirlukast



Montelukast



Zileuton

Leukotriene Pathway Modifiers

- **Churg-Strauss Syndrome:**

Rare reaction in newly treated asthmatic patients.

Severe inflammatory reaction, pulmonary infiltration, neuropathy, skin rash, and cardiomyopathy.

A common finding is systemic vasculitis with eosinophilic infiltration and granuloma formation.

Could also be due to unmasking of vasculitis after steroid withdrawal.

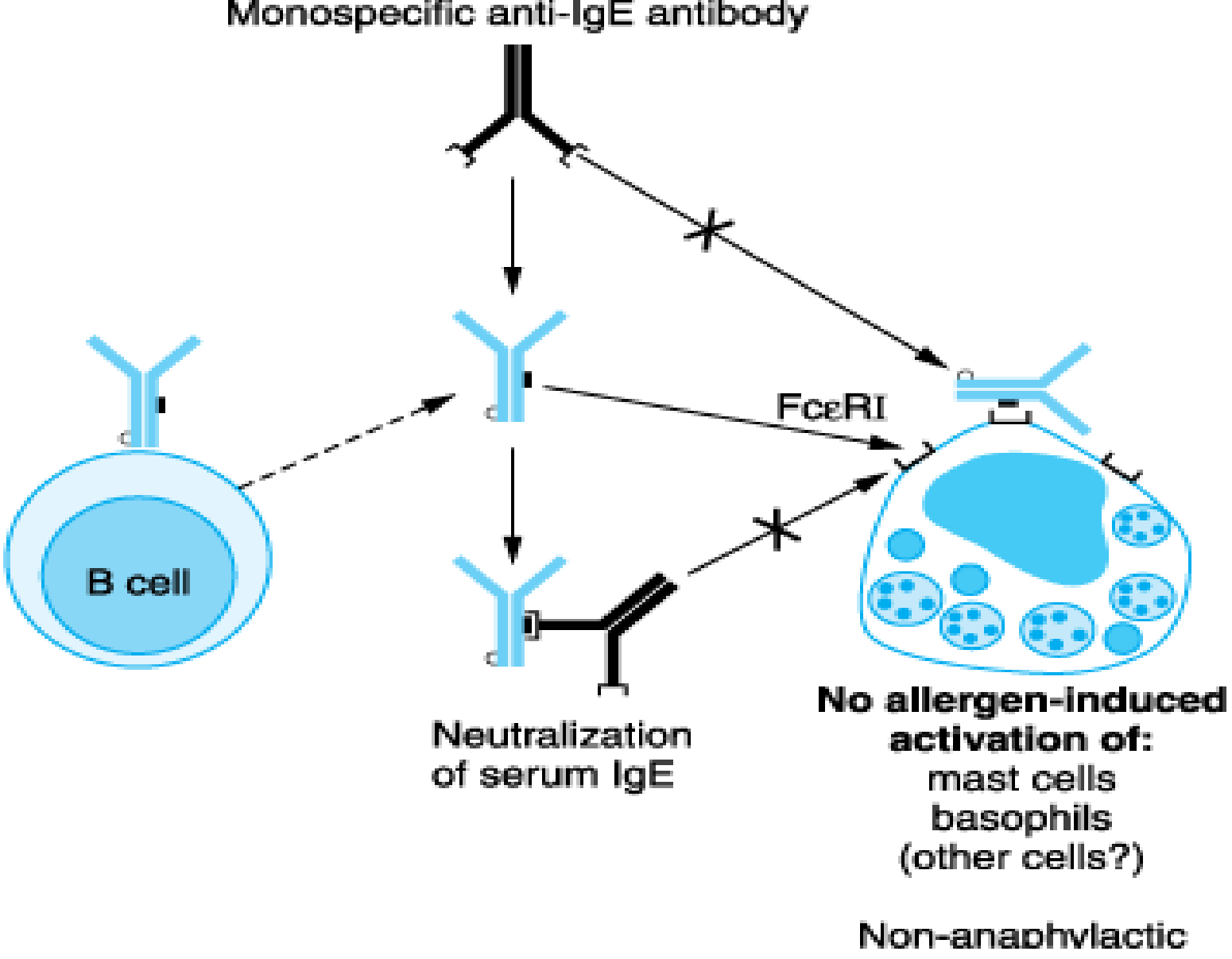
Montelukast / Beta agonist study

- ↓ percent of patients needing systemic use of corticosteroids by 39%
- ↓ in nighttime awakenings
- ↓ percent of patients having asthma attacks by 37%
- ↓ need for beta-agonists by 21%

Immunomodulating Biotherapeutics

Omalizumab:

- It is a humanized monoclonal anti-IgE antibody raised in mice.
- Not recognized as foreign by human immune system.
- Targeted against the portion of IgE that binds to its receptors (FC-R1 and FC-R2 receptors) on mast cells and other inflammatory cells.
- IgE-anti-IgE complexes are cleared from the blood without deposition in the kidneys or joints.
- Given as IV or SC injection every 2-4 weeks.



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Immunomodulating Biotherapeutics

- **Monoclonal antibodies directed against cytokines (IL-4, IL-5, and IL-13), antagonists of cell adhesion molecules, protease inhibitors, and immunomodulators aimed at shifting CD4 lymphocytes from the TH2 to the TH1 phenotype or at selective inhibition of the subset of TH2 lymphocytes directed against particular antigens.**

Possible Future Therapies

- **There is evidence that asthma may be aggravated—or even caused—by chronic airway infection with *Chlamydia pneumoniae* or *Mycoplasma pneumoniae*. This may explain the reports of benefit from treatment with macrolide antibiotics (erythromycins) and, if confirmed, would stimulate the development of new diagnostic methods and antimicrobial therapies.**

- **Feeding *Lactobacillus caseii* to infants born to allergic parents reduced the rate of allergic dermatitis at age 2 years, offers reason for hope.**

Status Asthmaticus

- **Life threatening exacerbation of asthma symptoms that is unresponsive to standard therapy, preceded by rapid increase in the daily use of bronchodilator drugs.**
- **Provocative factor usually present.**
- **Needs aggressive treatment in the hospital.**

Status Asthmaticus

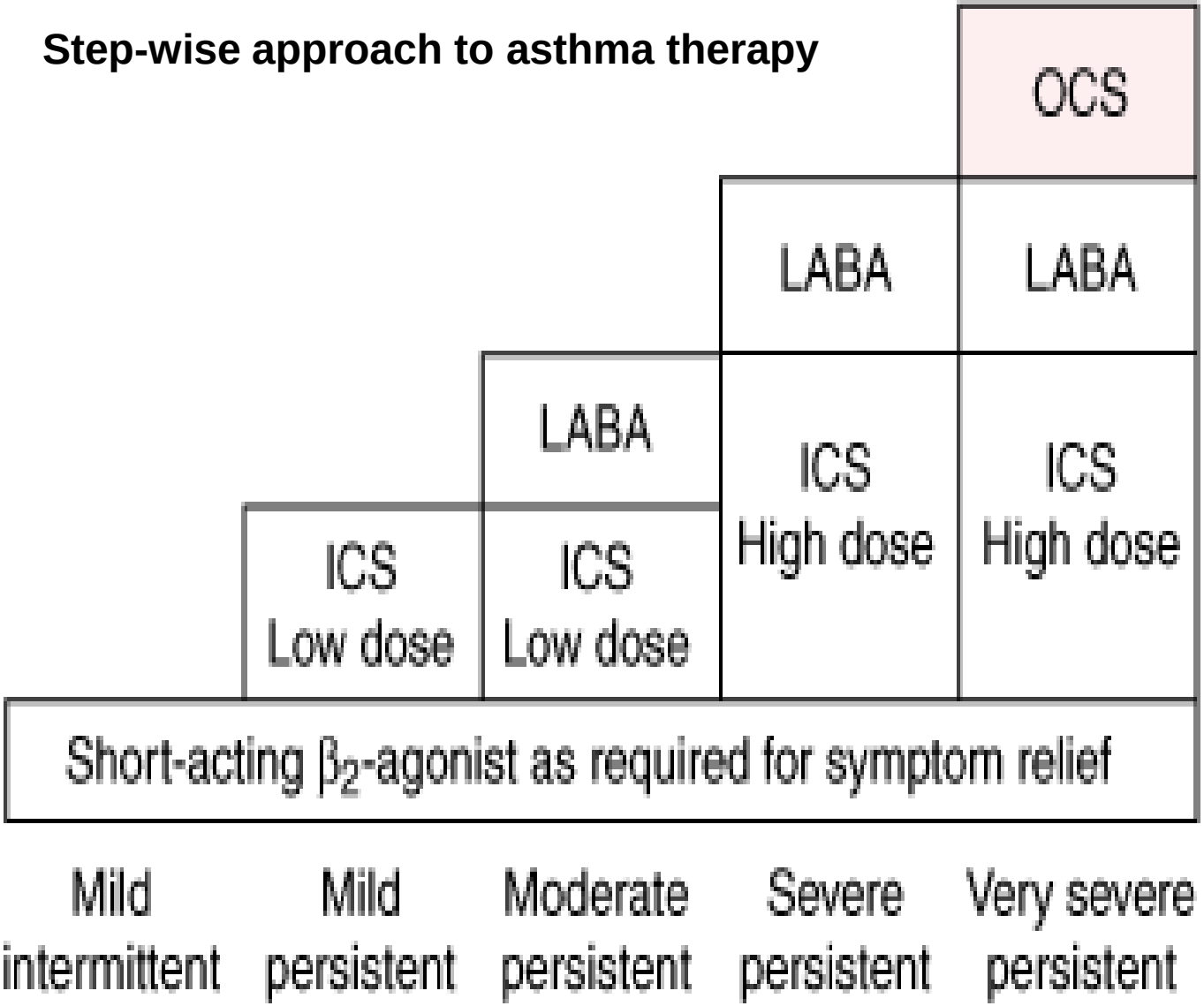
- **Oxygen.**
- **Inhaled short acting β2 agonists.**
- **Oral or Parenteral corticosteroids.**
- **Subcutaneous β2 agonists.**
- **Inhaled ipratropium maybe effective in some patients.**

Goal: No deaths on your watch

No patients should die of an acute episode of bronchoconstriction (an asthma attack) at any time, any place.

- **Aerosol therapy is available with hand held devices that operate on batteries.**
- **Even more immediate beta-agonist therapy via an “Epi-pen” is readily available.**

Step-wise approach to asthma therapy



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Conclusion

One day, in the future, doctors will know their patients genetic make-up and response to drugs such that they will be truly able to individualize their patient's therapy on the basis of fact – not guesswork or trial by error.

For now, they should individualize their patients therapy by therapeutic trial using the lowest dose that works and drugs in rational combinations.

RPL554

- **A unique inhaled drug, effective and well-tolerated as a bronchodilator, bronchoprotector, and anti-inflammatory drug in patients with chronic obstructive pulmonary disease (COPD) or asthma.**
- **RPL554 is a dual inhibitor, blocking the activity of 2 phosphodiesterase enzymes: phosphodiesterase 3 (PDE3) and PDE4.**