Treatment of Bronchial Asthma

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Definition of Asthma

Chronic inflammatory disorder with intermittent narrowing of the airways.

Characterized by wide variations, over short periods of time, in the resistance to flow in the intrapulmonary airways.

Factors in the Treatment Strategy

- **Asthma is a *chronic* condition**
- **The goal of therapy is *normal function***
- **Asthma 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

Deterioration of the condition.

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 ED 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 lead to bronchoconstriction.

Prevented by bronchodilators.

Pathogenesis

Late Asthmatic Response:

4-5 hours later.

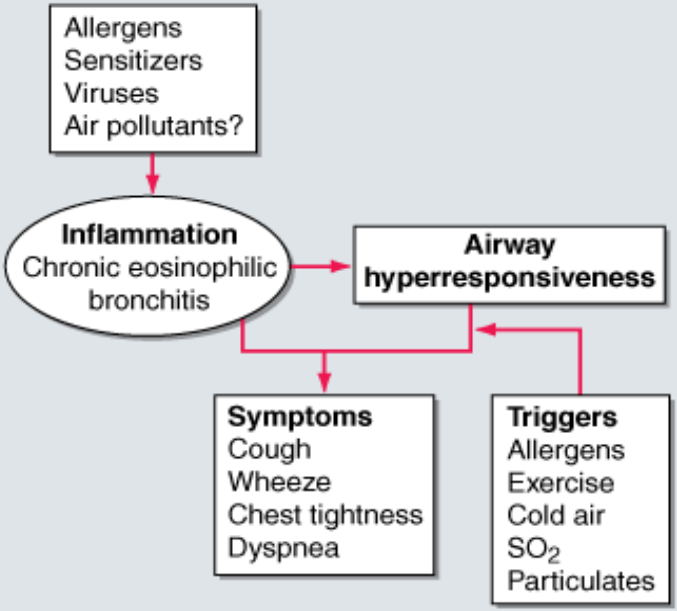
More sustained phase of bronchoconstriction.

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.



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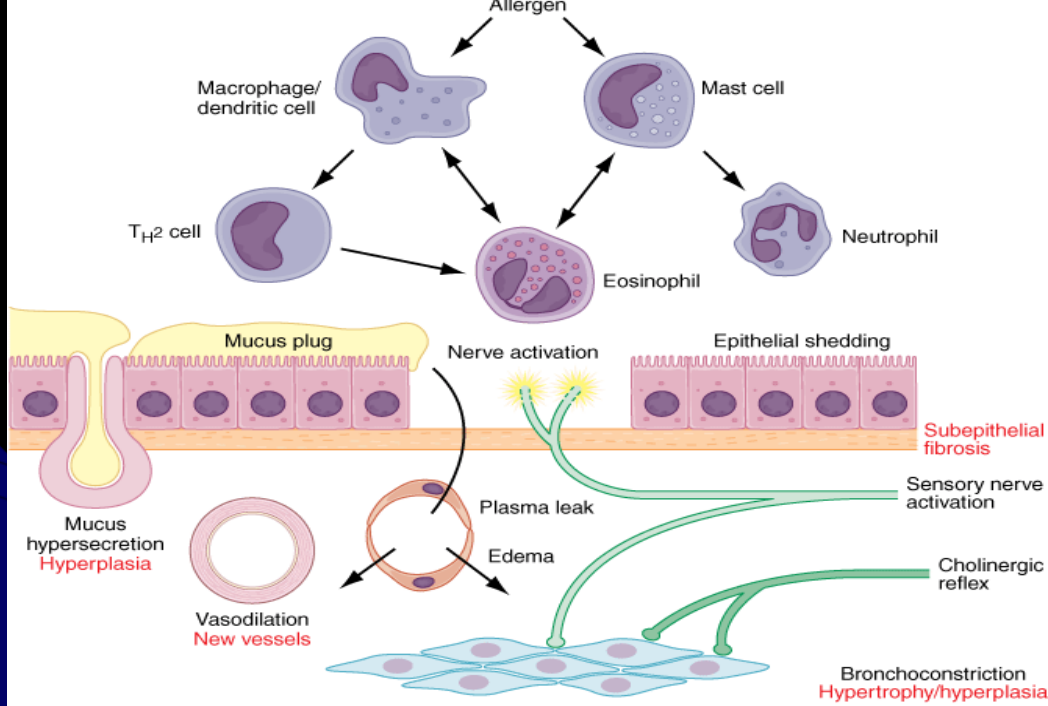

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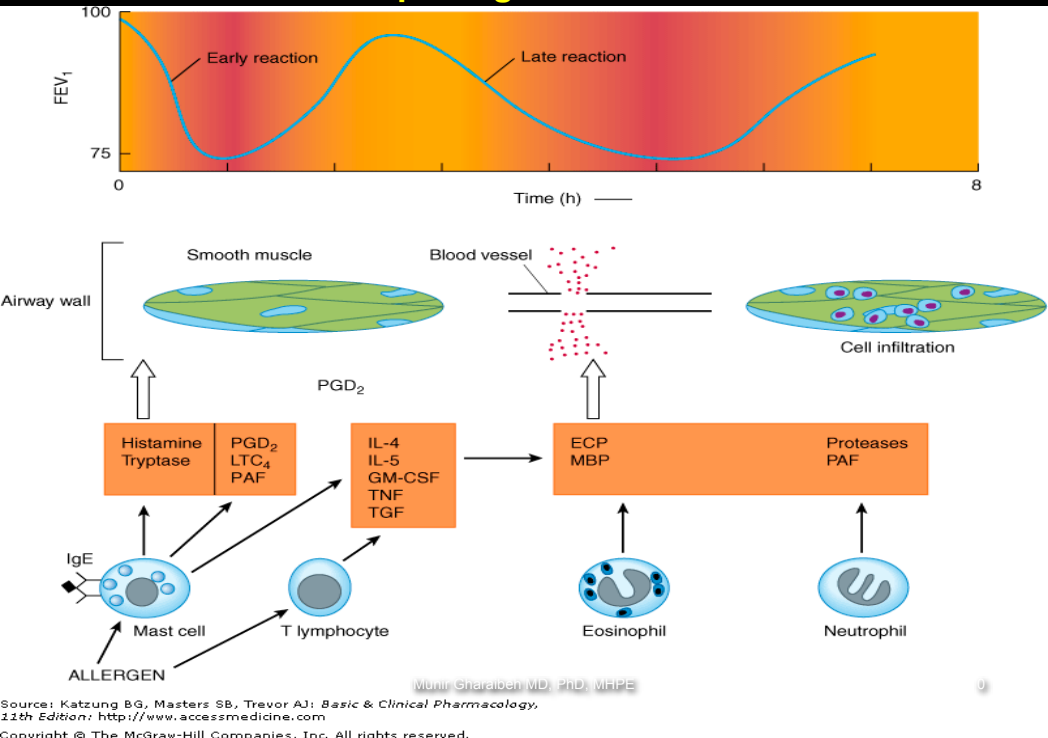
Immunopathogenesis of asthma.



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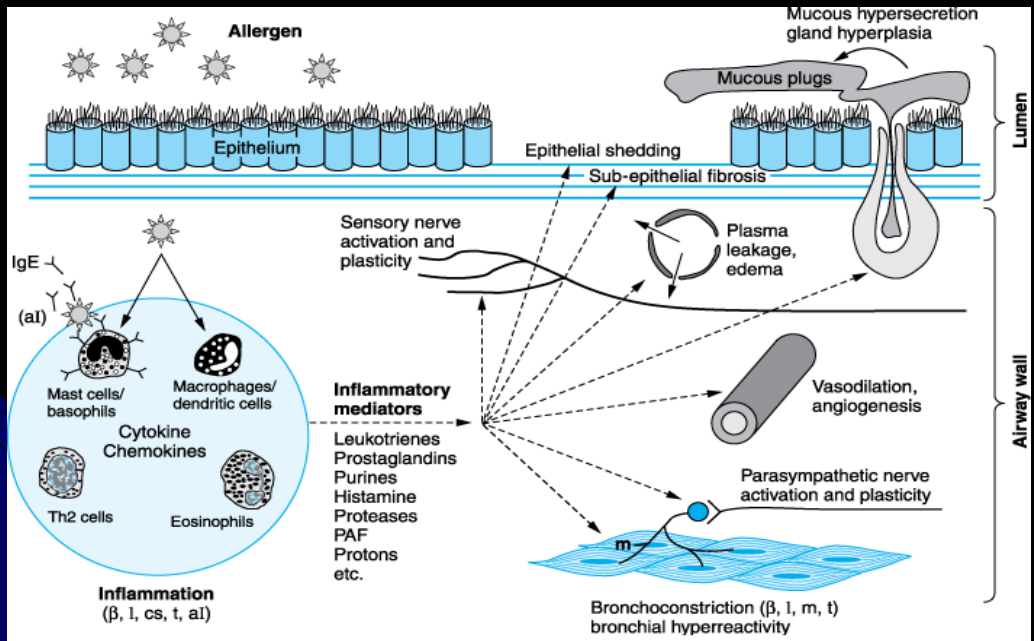
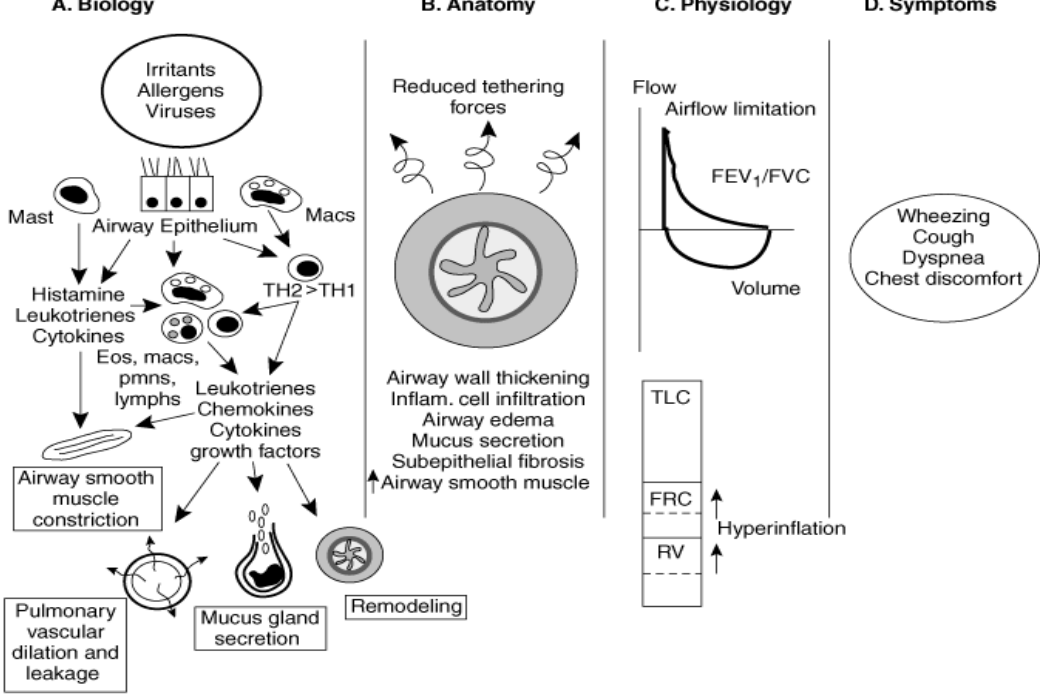
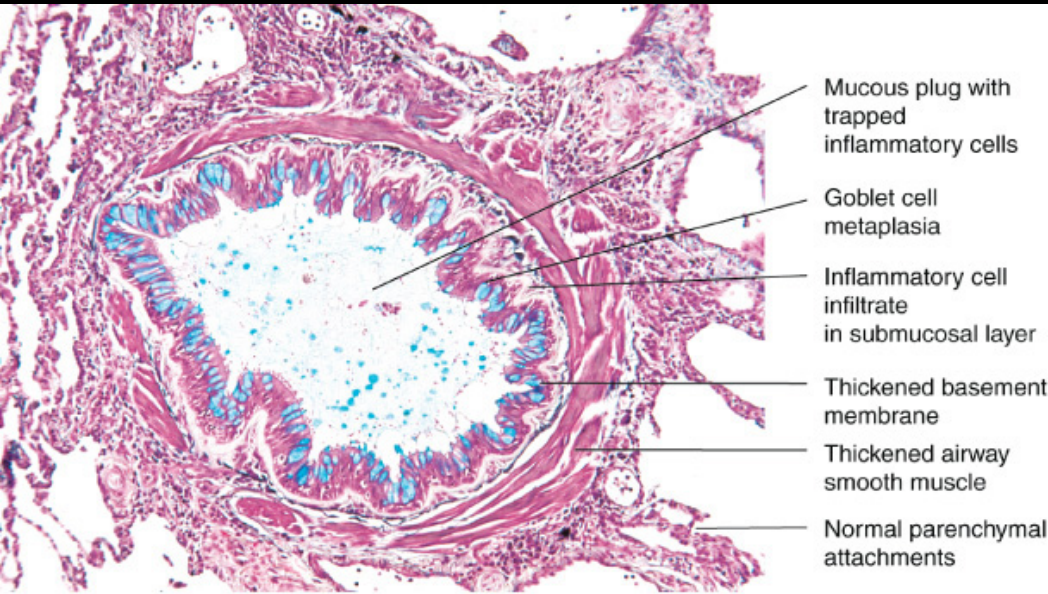
Simplified view of allergic inflammation in the airways.





Source: Hanley ME, Welsh CH: *Current Diagnosis & Treatment in Pulmonary Medicine*: http://www.accessmedicine.com

Histopathology of a small airway in fatal asthma



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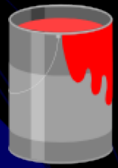
Asthma Triggers



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)

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, URI (common cold), or exposure to an allergen.**
- **Dyspnea > cough or wheezing > sputum.**
- **Past history of bronchiolitis as a child.**
- **Family history of asthma is common**

Diagnosis of Asthma - Objective

Reduced FEV_1 and FEV_1/FVC ratio

Reduced Peak 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.

Index of Severity

Peak Expiratory Flow Rate

	% Predicted	Lability (%)
Normal	> 90	< 10
Mild	70 - 90	10 - 20
Moderate	50 - 70	20 - 30
Severe	30 - 50	30 - 50
Very Severe	< 30	> 50

Overview 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

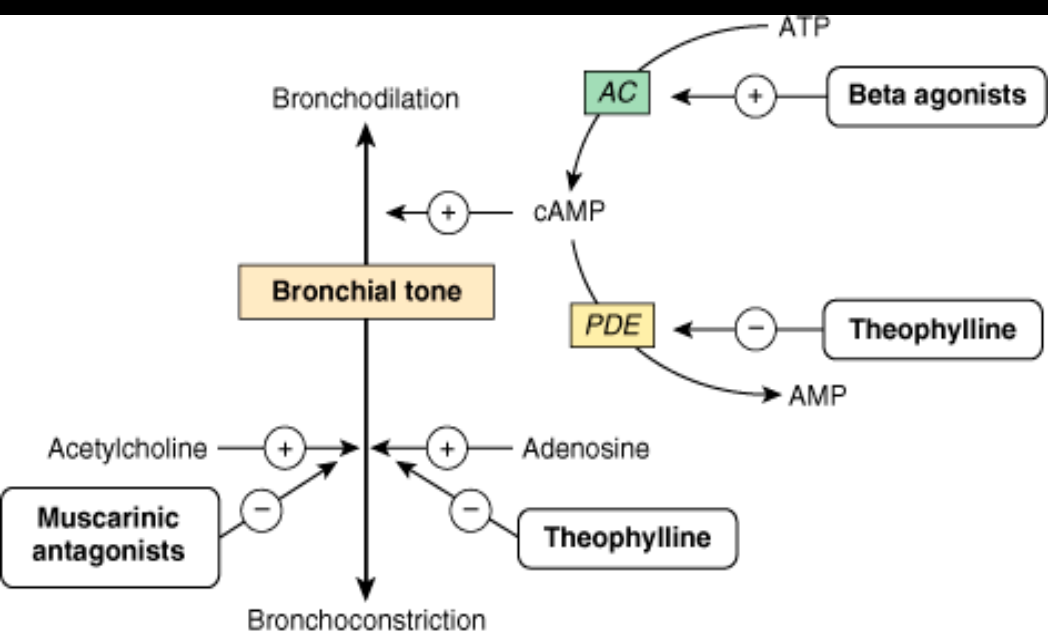
Survey of the changing therapy of asthma by decade

2000's

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

2010's

Prevention including gene therapy.



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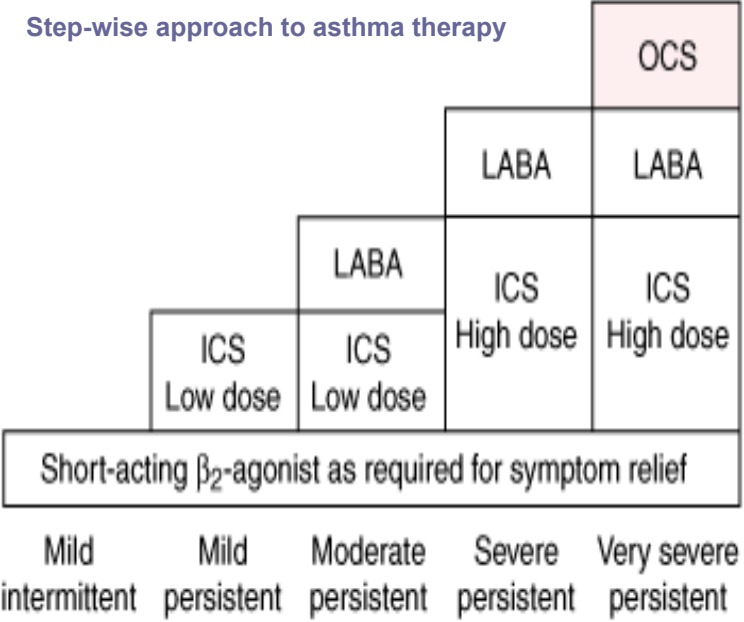
Step-wise approach to asthma therapy



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Relievers / Controllers

Quick relief medications:

- Inhaled Short acting Beta-2 Agonists
- Inhaled Anticholinergics
- Systemic Corticosteroids

Long-term control medications:

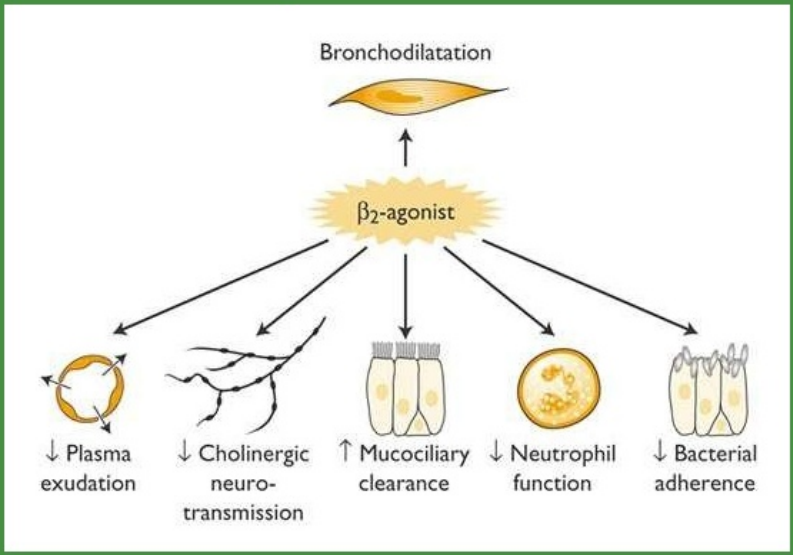
- Topical (inhaled) Corticosteroids
- Inhaled Cromolyn Na and Nedocromil
- Oral Methylxanthines (Theophyllines)
- Inhaled Long-acting Beta-2 Agonists (LABA)
- Oral Leukotriene modifiers (LTRA)

Beta 2-Adrenergic Agonists

Medications of choice for acute exacerbations

- Actively relax airway smooth muscle.
- Inhibit release of mediators.
- Enhance muco-ciliary activity.
- Decrease vascular permeability.
- Inhibit eosinophil activation.

Role of beta agonists in asthma and COPD



β2 agonists have other beneficial effects including inhibition of mast cell-mediator release, prevention of microvascular leakage and airway edema, and enhanced mucocillary clearance. The inhibitor effects on mast cell actions suggest that β2 agonists may modify acute inflammation.

Beta 2-Adrenergic Agonists

Molecular Actions:

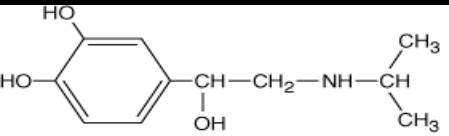
Increase cAMP.

Activate protein kinase A.

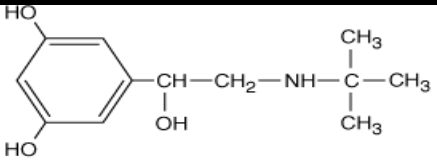
Phosphorylate kinases.

All lead to decreased cytosolic Ca++.

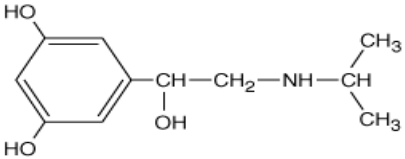
Beta2-Selective Drugs



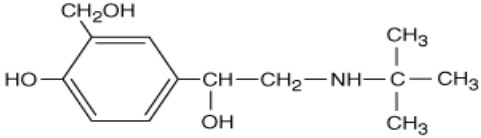
Isoproterenol



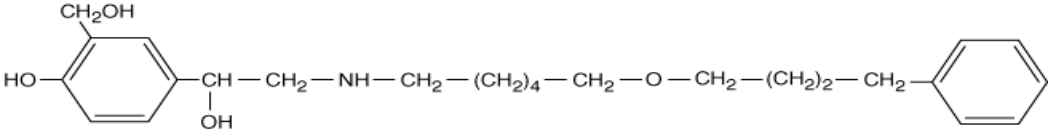
Terbutaline



Metaproterenol



Albuterol (salbutamol)



Salmeterol

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

Beta 2-Adrenergic Agonists

- **Epinephrine:**

Obtained from bovine adrenal gland.

Stimulates α, β1 and β2 receptors.

Not effective orally.

Subcutaneous.

Distribution and Actions of B1/B2 receptors

Organ	B1	B2
Heart	+ inotropic and chronotropic	
Blood Vessels		Vasodilation and Hypotension
Bronchi		Bronchodilation
Uterus		Tocolysis
Skeletal Muscles		Tremor
Fat tissue	Lipolysis (B3)	
Carbohydrate Metabolism		Glycogenolysis

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(Salbutamol).
Terbutaline.
Pirbuterol.
Metaproterenol.
Isoetharine.

Rapid onset: 3-5 minutes.
Maximal effect: 30-60 minutes.
Duration: 4-6 hours.

Long -acting Beta 2-Adrenergic Agonists(LABA)

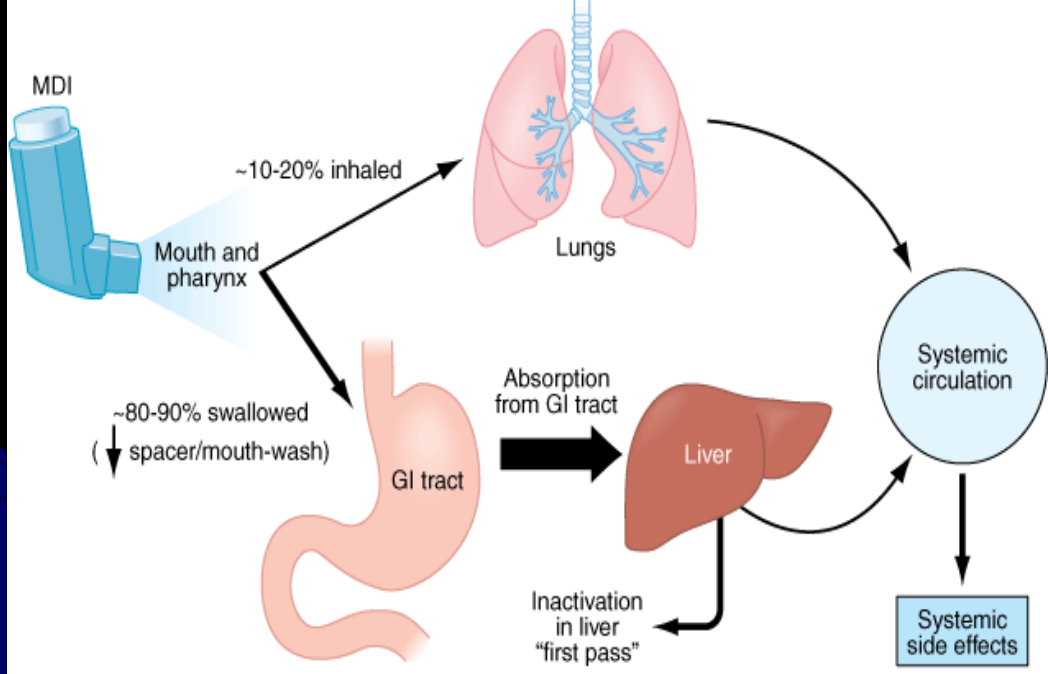
- Salmeterol.
- Formoterol.

Long-acting inhaled bronchodilators:12 hours.

Suppress nighttime attacks.

Controllers 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 in gets to the right place
- Inspiration too rapid - should take 4 - 5 seconds
- Nasal inspiration contains no medication
- Spacers not used, despite evidence of their great utility

➢ To use MDI's correctly requires instruction

Spacer

A large volume chamber attached to a MDI, used to decrease the deposition of drug in the mouth.

Serves to reduce the velocity of the injected aerosol before it enters the mouth and allows large drug particles to deposit in the device.

The smaller, high velocity drug particles, are more likely to reach the target airway tissue.

Rinsing the mouth can also decrease systemic absorption and oropharyngeal candidiasis.

Beta 2-Adrenergic Agonists

- Medications of choice for acute exacerbations
  - Actively relax airway smooth muscle
  - Enhance muco-ciliary 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

TOXICITY:

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.

"A Nested Case-Control of the Relation Between Beta-Agonists & Death and Near Death From Asthma"

All deaths and Beta agonist use were studied for 1 year.

As Beta Agonist use increased, risk of death increases.

For each canister per month increase in use, the risk of death doubled.

Conclusion:

Use of beta 2-Agonist drugs, as a class, is associated with an increased risk of death

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(60s-70s), withdrawn, then came back

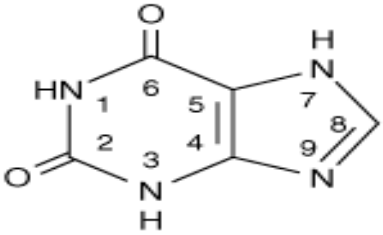
Oral, rectal, and Intravenous.

CNS stimulants

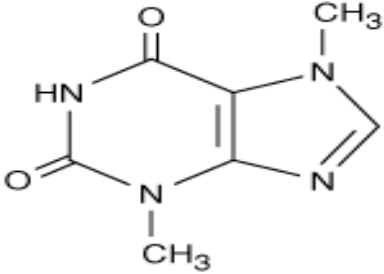
Cardiovascular stimulants; arrhythmias.

Nausea, GIT irritation, diarrhea.

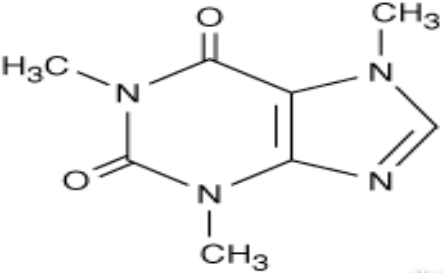
METHYLXANTHINE DRUGS



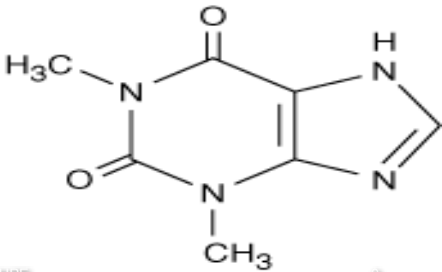
Xanthine



Theobromine



Caffeine



Theophylline

Mechanism of Action of Methylxanthines

- Phosphodiesterase inhibition.
- Adenosine receptor antagonism
  (adenosine causes bronchoconstriction)
- Antiinflammatory activity.

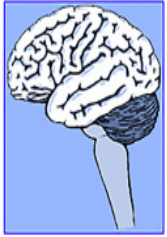
Methylxanthines

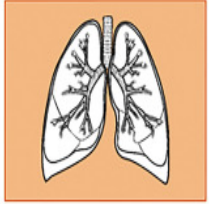
- Theophylline and its derivatives are most commonly used for the treatment of COPD and asthma.
- Caffeine, theophylline and theobromine are naturally occurring xanthine alkaloids which have qualitatively similar actions.

- ***Mechanism of action:***

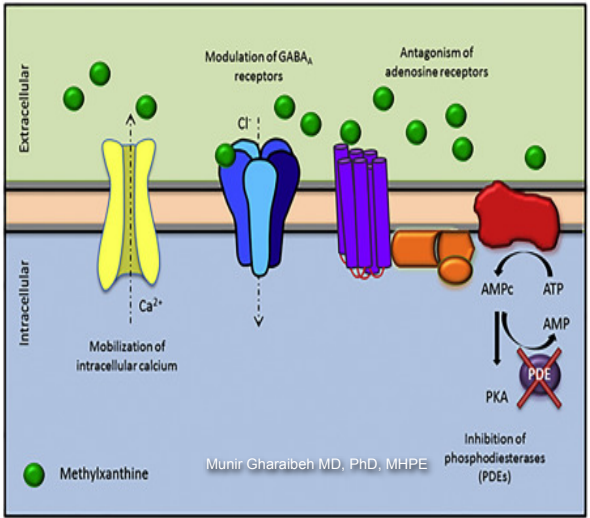
  – Methylxanthines inhibits cyclic nucleotide phosphodiesterase (PDEs), thereby preventing conversion of cAMP and cGMP to 5'-AMP and 5'-GMP, respectively. Inhibition of PDEs will lead to an accumulation of intracellular cAMP and cGMP. Bronchodilataion, cardiac stimulation and vasodilatation occur when cAMP level rises in the concerned cells. Theophylline and related methylxanthines are relatively nonselective in the **PDE subtypes inhibitor**.

  – Theophylline is a competitive **antagonist at adenosine receptors**. Adenosine can cause bronchoconstriction in asthmatics and potentiate immunologically induced mediator release from human lung mast cells. Methylxanthines inhibits the adenosine action thereby casing bronchodilataion.





Central control of respiratory function



- Bronchodilatation
- Decrease pulmonary arterial pressure
- Increase the airway diameter

Problems with Methylxanthines

- Therapeutic index is low.
- 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 around 36 µmol/ml (or 7 µg/ml), significantly inhibits the Late Asthmatic Reaction (LAR) and airway inflammatory infiltration.

Anticholinergic Agents

- **Atropine:**

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

Impairs mucociliary clearance leading to dryness, and consequently, 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 cytosol.

- Bind to cytosolic receptors.
- The drug-receptor complex enters the nucleus.
- 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:

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

Candida infection.

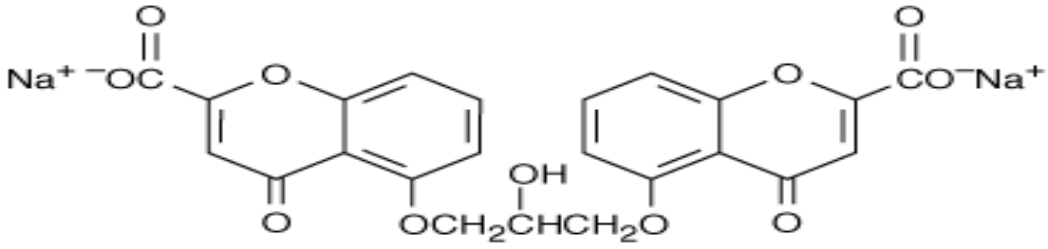
Systemic Side Effects:

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

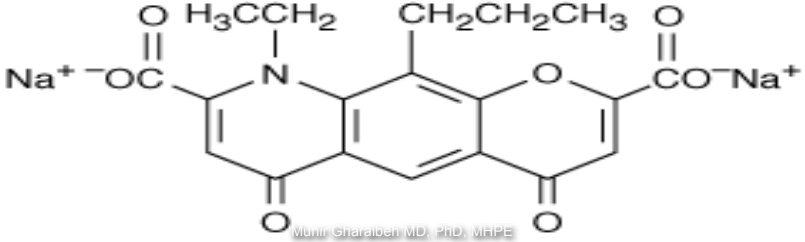
Inhibitors of Mast Cell Degranulation

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.
- Phosphorylate 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.

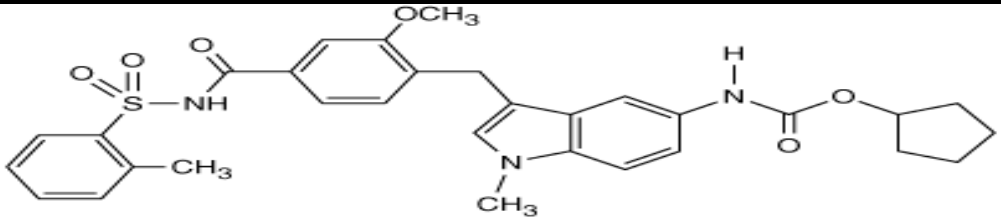
- **Antagonists of Cysteinyl Leukotriene Receptors:**

  Montelukast.

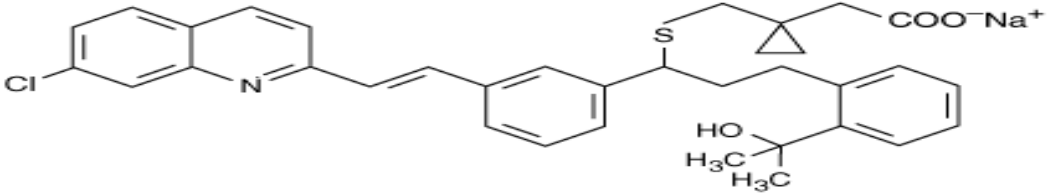
  Zafirlukast.

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

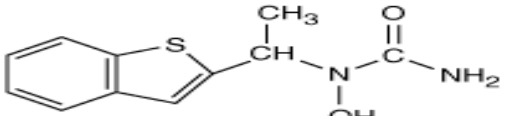
Leukotriene Pathway Inhibitors



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.

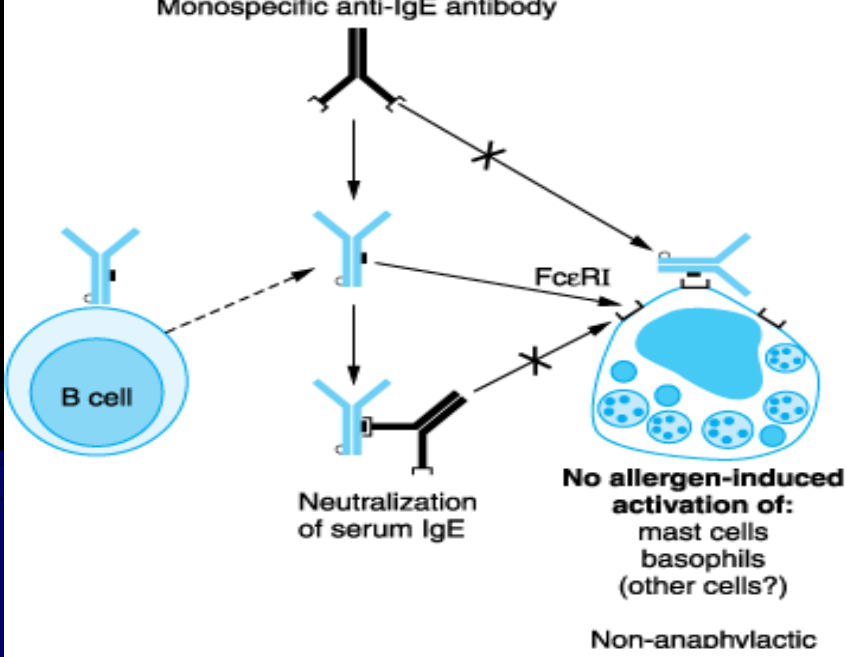
Montelukast / Beta agonist study

- 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.

General Therapy of Asthma

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

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).

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

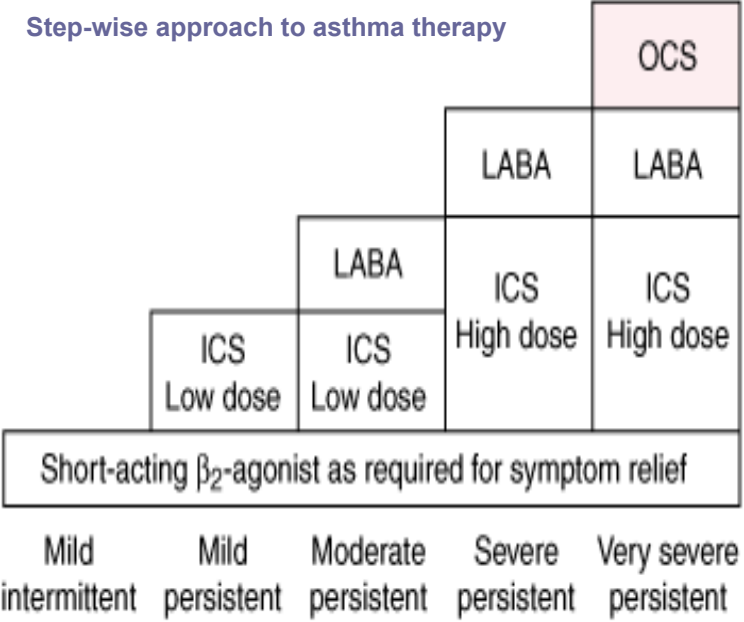
- Oxygen.
- Inhaled short acting β2 agonists.
- Oral or Parenteral corticosteroids.
- Subcutaneous β2 agonists.
- Inhaled ipratropium maybe effective in some patients.
- Epinephrin by s.c. injection.

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 handheld 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 patient's 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 patient's therapy by therapeutic trial using the lowest dose that works and drugs in rational combinations.

RPL554(Ensifentrine)

- **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.**