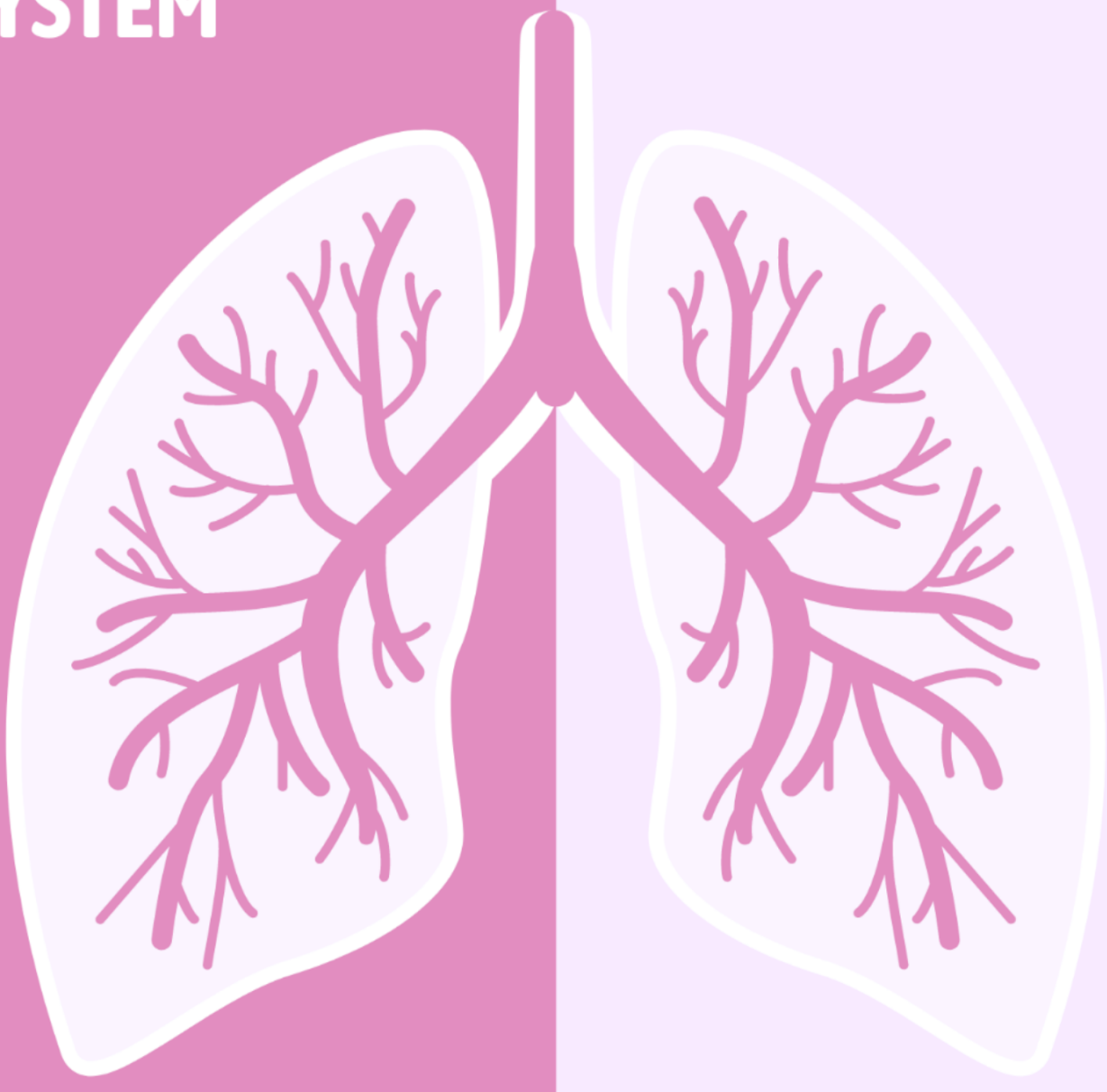
RESPIRATORY SYSTEM

PHARMACOLOGY



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ASTHMA

Definition of Asthma

- Episodic, 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.wide Variations of the cause of Asthma. Some people from the smoking others from Peanut.
  - Extent of bronchoconstriction and
  - Degree of inflammation.
- The course is unpredictable.
- Therapy must be individualized.

Risk of Not Treating Asthma Some patients improve spontaneously without treatment ,but that increase the risk for :

- 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%.
- FEV1 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 antigenantibody interaction on the surface of the mast cells leading to:

1. Release of stored mediators.
2. Synthesis of other mediators.
3. Also, activation of neural pathways.
4. All lead to bronchoconstriction.

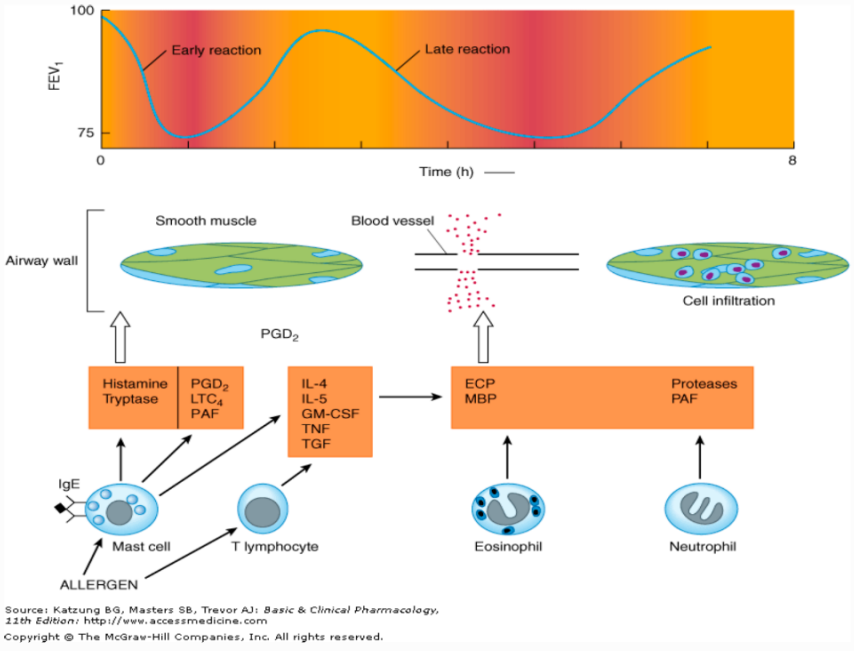
- Prevented by bronchodilators.

Late Asthmatic Response:

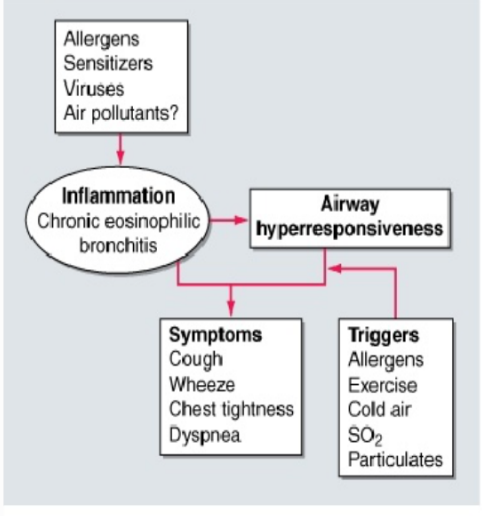
4-5 hours later.More sustained phase of bronchoconstriction.Influx of inflammatory cells and an increase in bronchial responsiveness.

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



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

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. (Acetyl salicylic Acid (Aspirin)), 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 FEV1 and FEV1/FVC ratio(using spirometry)
• Reduced Peak Expiratory Flow Rate (FEFR)
• Reversibility with Bronchodilators.if it is releaved by bronchodilator, then it is bronchial asthma.
• Heightened response to Methacholine Test.Methancholine is like Acetylcholine which induces bronchoconstriction.High response of Methancholine indicate bronchial Asthma.
• Increase in expired Nitric Oxide. NO → high in Inflammation
• Increase in Inflammatory mediators and their metabolic products in body fluids

Myths and Misconceptions

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

Index of Severity

	Peak Expiratory Flow Rate	
	% Predicted	Lability (%) (variability; It should be stable in normal people whenever they did the test)
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 therapyof Asthma by decade

1960s: Aminophylline, Epinephrine, Ephedrine.
1970's : Beta-agonists(Bronchodilator), Theophyllines, Beclomethasone, Cromolyn, Ipratropium
1980's : Beta-agonists, Inhaled ,Corticosteroids, Cromolyn, Ipratropium
1990's : Inhaled Corticosteroids, Betaagonists,Theophylline, Leukotriene Inhibitors
2000's :Corticosteroids + LABA, LTRAs,Theophylline, Cromolyn, Ipratropium, Tiotropium
2010's : Prevention including gene therapy.

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)

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.

1-Quick relief medications :-

A-Inhaled Short acting Beta-2Agonists ;they are taken in urgent situations because they make a quick and rapid dilation of the bronchial airways.

B- Inhaled Anticholinergics ;they alleviate the inflammation and the mucus secretion and support the process of bronchodilation.

C-SystemicbCorticosteroids ; they have an anti-inflammatory effect.

2-Long-term control medications (they prevent the asthmatic attacks and taken over a long period of time(NOT necessarily during the acute asthmatic attacks .they're taken whether we have an acute attack or not).
Depending on the patient's situation and depending on the severity of the asthma as well as the control on it , the patient may take along term control medications that are taken during or in the absence of the asthmatic attacks 🌚

A-Topical (inhaled) Corticosteroids

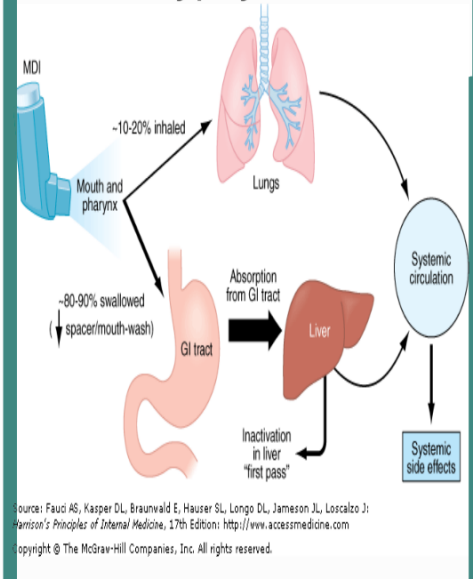
B-Inhaled Cromolyn Na and Nedocromil (they inhibit mast cells' activity , preventing the release of histamine thus alleviating the inflammation)

C-Oral Methylxanthines(Theophyllines) [it decreases the mucus secretion and thus alleviating the inflammatory process]

D-Inhaled Long-acting Beta-2 Agonists. (LABA) [they act for along period of time,they prevent the asthmatic attacks and keep the patient under control]

E-Oral Leukotriene modifiers (LTRA)(leukotriene receptor antagonists)[they have an anti-inflammatory and bronchodilation effect ,they prevent the recurrence of the asthmatic attacks]

So the treatment of asthma is divided into Short-acting and Long-acting medications, depending on the situation, and this doesn't mean that the patient only take one of the two groups .For example, the patient might take a drug form the first group for the acute attacks and from the second group for the prevention of the following attacks.

Mild intermittent	Mild persistent	severe persistent
Drug of choice Short-acting beta-2- agonist (required for symptom relief Increase cAMP→ Activate protein kinase A→ Phosphorylate kinases.→ All lead to decreased cytosolic Ca++	short acting B2-Agonist+ Inhaled Corticosteroids in low doses (ICS)	Short acting Bz agonist as required for Symptom relief . + high dose Cortico steroid + LABA
Moderate persistent		very severe persistent
• Drugs: • Epinephrine: Obtained from bovine adrenal gland. Stimulates α, β1 and β2 receptors. Not effective orally. Subcutaneous • Isopreterenol: Stimulates β1 and β2 receptors. First (1960s) convenient, pocket- sized multidose inhalers. Considerable tachycardia and pounding • Short acting Beta2 Adrenergic Agonists (Drug of choice to relief Symptoms) ● Albuterol(Salbutamol). ● Terbutaline. ● Pirbuterol. ● Metaproterenol. ● Isoetharine. Rapid onset: 3-5 minutes. Maximal effect: 30-60 minutes. Duration: 4-6 hours. •	short acting Bz - agonist + ICS (low Doses)+long acting B-Agonist. Long acting Beta2 Adrenergic Agonist drugs ● Salmeterol. ● Formoterol. Long-acting inhaled bronchodilators:12 hours. Suppress nighttime attacks. Controllers with steroids. No tachyphylaxis.  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 Copyright © The McGraw-Hill Companies, Inc. All rights reserved.	Short acting Bz agonist as required for Symptom relief . + high dose Cortico steroid + LABA+Oral corticosteroid (OCS)

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 January

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

⚫ 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.

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