Treatment of Cough

*** Specific Treatment of Cough (*Directed on the etiology or pathophysiological mechanism) :***

Bronchial Asthma , Postnasal drip due to sinusitis , Postnasal drip due to allergic or perennial non allergic sinusitis, Gastroesophageal Reflux(GERD), Chronic bronchitis, Sarcoidosis , Congestive heart failure , ACEI-induced cough.

***Nonspecific Treatment of Cough (Directed at the symptom) :**

- Indicated when definitive therapy cannot be given either because the cause is unknown or the definitive therapy did not have the chance to work or will not work(e.g. cancer metastatic to lung).

1) Antitussive Drugs:

- therapy that controls, inhibits or eliminates cough. Useful to suppress intensity and frequency of coughing when it is unproductive and distressing.

A) Drugs that may alter mucociliary factors

- Increase the volume of the secretions.
- Decrease the production of mucus.
- Change the consistency of mucus (i.e. Mucolytics).
- Increase mucociliary clearance.

* **Ipecacuanha and Squill** (natural products) **:** have direct effects on CNS and locally to cause emesis.

* **Volatile oils:** have direct action on bronchi.

* **Iodinated glycerol :** - Excreted through bronchial glands and stimulates secretions directly.
- Can cause congenital hypothyroidism
- Contraindicated in pregnancy and during lactation

* **Bromhexine:** increases lysosome activity leading to increased enzyme secretion and hydrolysis of mucopolysacharides.

***Carbocisteine:** an aerosol, works through its SH group to reduce disulfide bonds in mucoproteins leading to enhancement of flow , May irritate the airways in some sensitive patients.

***Ammonium chloride** ***Hydration: either orally or intravenously**

***Combination of H1-histamine antagonist and a decongestant**

*** Ipratropium bromide ,Beta adrenergic agonists, Theophylline, Sodium chromoglycate, Beclomethasone.**

B) Drugs acting on the afferent limb.

*** Local anesthetics** (**Lidocaine**): applied topically, has transient antitussive effect. Intravenously, could have a central effect.

*** Opioids**

C) Drugs acting on the cough center.

1) Narcotics:

*** Codiene:** Is the standard, recently found no more effective than syrup vehicle. May have demulcent activity.

*** Diamorphine** *** Morphine**

2) Non narcotic: (Dextromethorphan, Glaucine, Diphenhydramine, Pholcodine).

D) Drugs acting on the efferent limb.

*** Ipratropium Bromide :**

- Given as an aerosol .
- Effective for asthma, chronic bronchitis, and persistent cough following URTI.
- Can also have effects on cough receptors by altering mucociliary factors

E) Drugs acting on the respiratory skeletal muscles

* **Pancuronium** (Nondepolarizing blocker)

- May be considered in patients who can not be mechanically ventilated because of uncontrollable spasms of coughing.

2) Protussive Drugs:

- Therapy that makes cough more effective.
- Increases cough effectiveness with or without increasing cough frequency.
- They either increase superficial velocity or alter mucus factors.
- Indicated when cough performs a useful function, and needs to be encouraged(e.g. bronchiectasis, cystic fibrosis, pneumonia and postoperative atelectasis).

* **Hypertonic Saline Aerosol :** Improves cough clearance but not pulmonary function or subjective assessment.

* **Amiloride Aerosol :** For cystic fibrosis .

* **Bronchodilators:** Flow rates may actually decrease with too much relaxation.

Antituberculous Agents

1) Primary or First Line Drugs:

A) Isoniazid (INH)

- Most active - Prodrug, activated by KatG, the mycobacterial catalase-peroxidase
- Readily absorbed - Metabolized by acetylation
- **Adverse Reactions:** Hepatitis, Neuropathy, Neurotoxicity

B) Rifampin "Rifadin" or "Rimactane"

- Bactericidal - Hepatic metabolism and exhibits enterohepatic recirculation
- **Uses :** TB, Leprosy, Meningococcal Carrier State, Prophylaxis in *H.influenzae,* Serious Staph osteomyelitis and valve endocarditis.
- **Toxicity :** Imparts harmless orange color to secretions(tears, urine, sweat) , Nephritis, Rashes Hepatitis, Flu-like syndrome, Liver Enzyme Inducer so can lower serum levels of many drugs.

C) Streptomycin

- **Uses:** Plague, Tuleremia, Brucellosis ,Endocarditis.
- **Toxicity :** Allergy: Fever, Rashes, Vestibular toxicity, Nephrotoxicity.

D) Pyrazinamide

E) Ethambutal

2) Secondary or Second Line Drugs

*__Indications for Secondary or Second Line Drugs:__

1. Resistance to first –line drugs. 2. Failure of clinical response to conventionalν therapy.
3. Occurrence of serious treatment-limitingν adverse drug reactions.
4. When expert guidance is available to dealν with the toxic effects.

A) Ethionamide

- Related to Isoniazid - Blocks mycolic acid synthesis
- Poorly tolerated: Severe GIT irritation, Neurotoxic, Hepatotoxic

B) Capreomycin

- Peptide protein synthesis inhibitor - Injectable - Nephrotoxic, ototoxic
- Local pain and sterile abscesses may occur.

C) Cycloserine:

- Inhibits cell wall synthesis.
- Peripheral neuropathy and CNS toxicity including depression and psychotic reactions.

D) Para-Amino-Salicylic Acid (PAS):

- Folate synthesis antagonist, Well absorbed, Excreted in urine, GI toxicity, Hypersensitivity reactions, Crystalluria

E) Amikacin

- For Multidrug-resistant strains Atypical mycobacteria

F) Flouroquinolones

G) Linezolid:

- Multidrug-resistant strains, Bone marrow suppression, Irreversible peripheral and optic neuropathy , Drug of last resort.

H) Rifabutin, Rifapentine

- Related to Rifampin , Inhibit bacterial RNA polymerase
- inducers for CYP P450 enzymes.
- Rifabutin is indicated in place of Rifampin in the treatment of TB in HIV-infected patients receiving protease inhibitor or nonnucleoside reverse transcriptase inhibitor (e.g. efavirenz).

Regimen (in Approximate Order of Preference)	Duration in Months
Isoniazid, rifampin, pyrazinamide	6
Isoniazid, rifampin	9
Rifampin, ethambutol, pyrazinamide	6
Rifampin, ethambutol	12
Isoniazid, ethambutol	18
All others	≥24

***Atypical Mycobacteria (Nontuberculus Mycobacteria)**

10% of clinical isolates, Distinctive laboratory characteristics, Present in the environment, Not communicable from person to person, Less susceptible to drugs.

M.tuberculosis complex: Erythromycin+ Sulphonamides + Tetracycline

M.avium complex: Important and common cause of disseminated TB in late stages of AIDS. **Azithromycin /Clarithromycin+ Ethambutal + Ciprofloxacin**

Drug-Resistant TB (3)

Mono-resistant	Resistant to any one TB treatment drug
Poly-resistant	Resistant to at least any 2 TB drugs (but not both isoniazid and rifampin)
Multidrug resistant (MDR TB)	Resistant to at least isoniazid and rifampin, the 2 best first-line TB treatment drugs
Extensively drug resistant (XDR TB)	Resistant to isoniazid and rifampin, PLUS resistant to any fluoroquinolone AND at least 1 of the 3 injectable second-line drugs (e.g., amikacin, kanamycin, or capreomycin)

Treatment of Bronchial Asthma

- Asthma is a **chronic inflammatory disorder** with intermittent narrowing of the airways or conditon characterized by wide variations over short periods of time **in the resistance to flow** in the intrapulmonary airways.

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

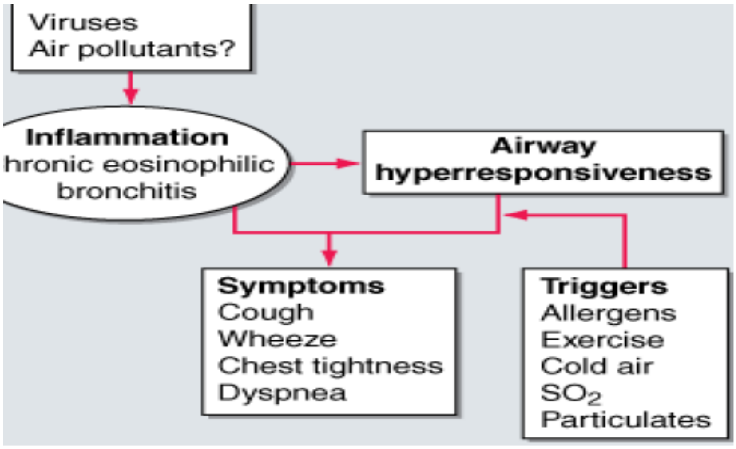
- Risk of Not Treating Asthma:
Poor or no control of the patient's asthma,Accelerated decline in the function of the patient's lungs as measured by PFT's , Increased number of attacks of asthma, Poorer response to therapy if started late, Increased mortality from asthma.

- Goals of Therapy in Asthma:

1. Minimal symptoms even during sleep. No, or infrequent, acute episodes.
2. No emergency visits or missed days in school or work.
3. Rare need for beta-agonist inhaler therapy.
4. No limitation of activities – even sports.
5. Peak flow rate variability less than 20%.
6. FEV1 consistently >80% of predicted range.
7. No or minimal adverse effects from drugs.

- Pathogenesis
Early Asthmatic Response: can be Prevented by bronchodilators.
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, activation of neural pathways, All will result in bronchoconstriction .

Late Asthmatic Response: can be Prevented by corticosteroids.
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.



- 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**

1) 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

2) Objective
Diminished Peak Expiratory Flow Rate (PEFR)
Reduced FEV1 and FEV1/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

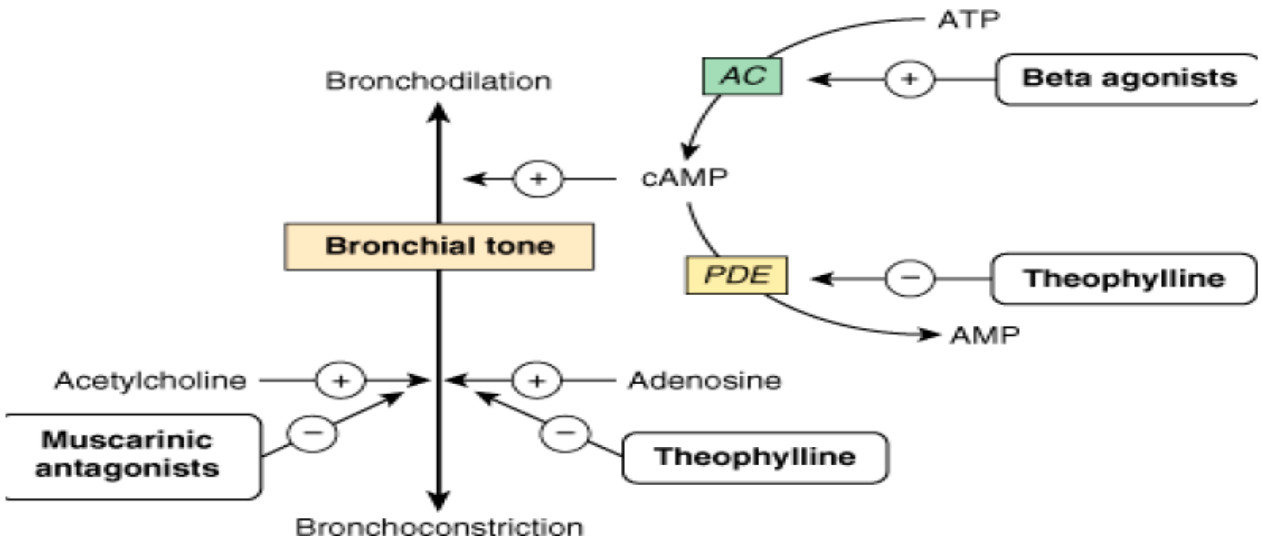
1970's: beta-agonists, theophyllines, beclomethasone, cromolyn, ipratropium

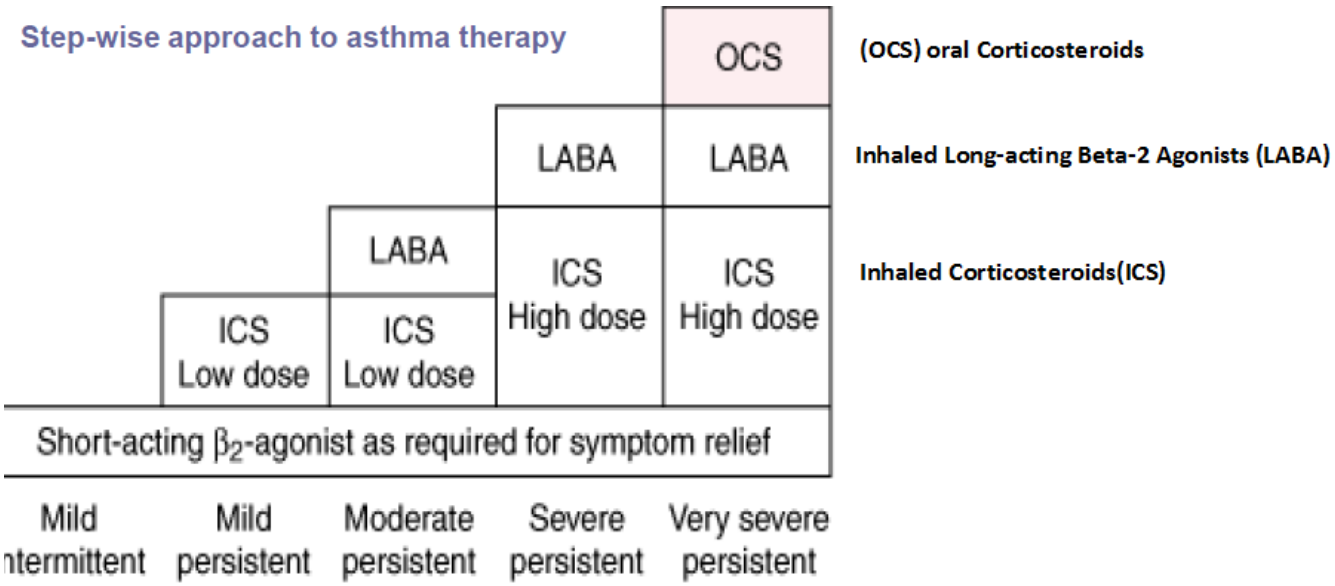
1980's: beta-agonists , inhaled cortico steroids, cromolyn, ipratropium

1990's: inhaled cortico steroids, beta-agonists, theophyllines , leukotriene inhibitors

2000's: corticosteroids +LABA (Inhaled long acting b2 agonists) , LTRAs , theophyllines, cromolyn, ipratropium, tiotropium

2010's: prevention including gene therapy





* **General Therapy of Asthma :** Oxygen, Hydration, Expectorants(مقشعات), Antimicrobials .

****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.

1) Pharmacological Actions: Bronchodilation, Tremor, Tachycardia, Fall in blood pressure. Slight fall in plasma potassium.
2) Molecular Actions: Increase cAMP, Activate protein kinase A , Phosphorylate kinases, All lead to decreased cytosolic Ca++.

* **Relievers / Controllers of Asthma :**

A) Quick relief medications:

1) Inhaled Short acting Beta-2 Agonists
(Albuterol, Terbutaline, Pirbuterol, Metaproterenol, Isoetharine)
- Beta 2 selective, Rapid onset: 3-5 minutes , Maximal effect: 30-60 minutes, Duration: 4-6 hours .

2) Anticholinergics (Atropine)

3) Systemic Corticosteroids

B) Long-term control medications:

1) Topical (inhaled) Corticosteroids
2) Inhibitors of Mast Cell Degranulation
3) Oral Methylxanthines
4) Inhaled Long-acting Beta-2 Agonists (LABA)
5) Oral Leukotriene modifiers (LTRA)
a) Inhibitors of 5-Lipoxygenase enzyme
b) Antagonists of Cysteinyl Leukotriene Receptors

***Notes:**

- **Beta 2-Adrenergic Agonists** are Medication of choice for acute exacerbations.

- **Beta 2-Adrenergic Agonists** decrease cytosolic Ca++.

- **Epinephrine** used in status asthmaticus and patients not responding to normal treatment .

- **Beta 2-Adrenergic Agonists** Toxicity: Nervousness, Anxiety, Tremor , Tachyphylaxis , cardiac toxicity.