- RS Pharmacology -
- Done by: Ola Alahdab -

LEC 1: COUGH THERAPY:

Cough is a symptom of an underlying illness.

It is a protective reflex elicited by:

- **Mechanical stimulation** of large respiratory passages, by foreign bodies or inflammatory exudates or debris.
- **Chemical stimulation** of alveoli.
- After receptor activation, impulses are carried through **afferent vagal nerves** to a medullary center to initiate deep inspirations, followed by strong expiratory effort against closed glottis leading to increased pressure in the airways. Glottis suddenly relaxes, mouth opened, and air is released at high pressure.
- Cough is one of the most common reasons patients see physicians, it might indicate: Something is wrong; **exhaustion**, **insomnia (+ diabetes + HTN + obesity)**, **musculoskeletal** pain, **hoarseness** of voice, **urinary** incontinence, **dizziness**, **headache**, **syncope**, **nausea**, **vomiting**, **retching**, & **anorexia**, fear of **cancer**, **AIDS**, or **TB**.

- 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.
Chronic bronchitis.
Gastroesophageal Reflux (GERD).
Sarcoidosis.
Congestive heart failure (due to pulmonary congestion).
ACEI-induced cough (drug-induced).

- Non-specific Treatment of Cough:

Directed at the symptom & indicated when definitive therapy can't be given either because: a. the cause is unknown b. definitive therapy did not have the chance to work or will not work (e.g. cancer metastatic to lung).

- Treatment of Cough is divided into two main categories:

a. **Anti-tussive Drugs** ضد القحة: therapy that controls, inhibits or eliminates cough. Useful to suppress intensity and frequency of coughing when it is unproductive and distressing.

b. **Pro-tussive Drugs** تشجّع القحة: therapy that makes cough more effective, when it is productive, to expel a foreign body or exudates.

We have 2 types of cough, productive (wet) cough and unproductive (dry) cough.
- wet cough serves the purpose of expelling the foreign body or the inflammatory exudate. So there's importance of productive cough.
- dry cough usually doesn't serve any purpose. (it has no purpose, it's just irritative)
So, if it's dry cough -> we suppress it. If it's wet cough -> we encourage it.

We have to suppress the dry cough & encourage the sputum cough.

- Drugs for Cough:

1) Drugs that may alter mucociliary factors:

– Increase the volume of the secretions.
– Change the consistency of mucus (i.e. **Mucolytics**).
– Increase mucociliary clearance (drugs that stimulate cilia).

- **Ipecacuanha** عرق الذهب & **squill** بصل الفار:

- Natural products, have direct effects on CNS & locally to cause **emesis** which is preceded by increased secretions. (Cough & emesis have the same neural pathway).

• **Volatile oils** الزيوت الطيارة (e.g., lemon, anise اليانسون, pine الصنوبر), have direct action on bronchi.

• **Iodinated glycerol**: is excreted through bronchial glands and stimulates secretions directly. Widely used but have doubtful efficacy. **Can cause congenital hypothyroidism, so contraindicated in pregnancy and during lactation**.

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

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

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

• **Ammonium chloride**.

• **Hydration**: orally or IV.

• **Ipratropium bromide**.

• **Beta adrenergic agonists**.

• **Theophylline**.

• **Sodium chromoglycate**.

• **Beclomethasone**.

Bronchodilators.

"These drugs are discussed in the treatment of bronchial asthma."

2) **Drugs acting on the afferent limb:** (work on nerves)

– **Local anesthetics** المخدرات الموضعية:

• **Lidocaine:** applied topically بخّاخ, has transient antitussive effect. If given IV it could have a **central** effect.

– **Opioids**: cough inhibitors, beside their primary **central** effect.

3) **Drugs acting on the cough center:**

- **Narcotics أدوية مخدّرة**:

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

لا يُستعمل كمسكّن، ولكنه يثبّط ال COUGH

• **Diamorphine**.

• **Morphine**.

Used in terminal patients

- **Non-narcotic**:

• **Dextromethorphan**.

• **Glaucine**.

• **Diphenhydramine**.

• **Pholcodine**

4) Drugs acting on the efferent limb:

– **Ipratropium Bromide**

Recall that sympathetic causes bronchodilation,
parasympathetic causes bronchoconstriction,
So, antiparasympathetic (parasympatholytic) like atropine causes bronchodilation

Anti-cholinergic (**atropine-like** drug).

• Given as an aerosol.

• Effective for asthma, chronic bronchitis (COPD), & persistent cough following URTI.

• Can also have effects on cough receptors by altering **mucociliary** factors.

5) Drugs acting on the respiratory skeletal muscles: (muscle relaxants)

– Non-depolarizing blockers like **pancuronium**.

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

- Protussive Therapy:

• This treatment **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, & needs to be encouraged (e.g. bronchiectasis, cystic fibrosis, pneumonia & postoperative atelectasis).

• **Hypertonic (3%) Saline Aerosol**: تبخيرة مي وملح

– Improves **cough clearance** but not pulmonary function or subjective assessment.

• **Amiloride Aerosol**:

– For **cystic fibrosis**. (Mainly it is a diuretic).

• **Bronchodilators**:

– However, with too much relaxation, **flow rates may decrease**.

- **Mechanical Measures**: العلاج الطبيعي

– **Positive insufflation** followed by **manual compression** of the **lower thorax & abdomen**.

– **Abdominal push** manoevure to assist expiration.

– Combining **abdominal binding** حزام للضغط على البطن **& muscle training** of the clavicular portion of pectoralis major.

– Combination of **positive expiratory pressure & chest physiotherapy** in patients with chronic bronchitis.

Lec 2: ASTHMA THERAPY:

Asthma is a 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 chronic.

➢Asthma is heterogeneous in terms of:

- Cause or trigger mechanism.
- Extent of bronchoconstriction.
- Degree of inflammation.

➢The course is unpredictable.

➢Therapy must be individualized.

- Risk of Not Treating Asthma:

1) Deterioration of the condition.
2) Accelerated decline in PFT's.
3) Increased number of asthma attacks.
4) Poorer response to therapy if started late.
5) Increased mortality from asthma.

- Early Asthmatic Response:

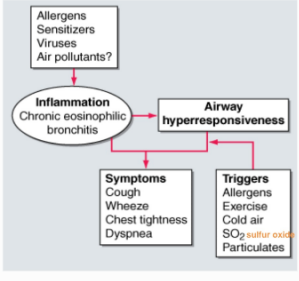
Prevented by bronchodilators.

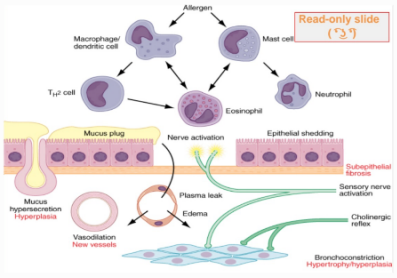
- Late Asthmatic Response:

Prevented by corticosteroids.

- 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.





- 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 (aspirin), NSAID's, others).

- Myths & Misconceptions: خرافات

✓ Patient & 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.

- Subjective Diagnosis of Asthma:

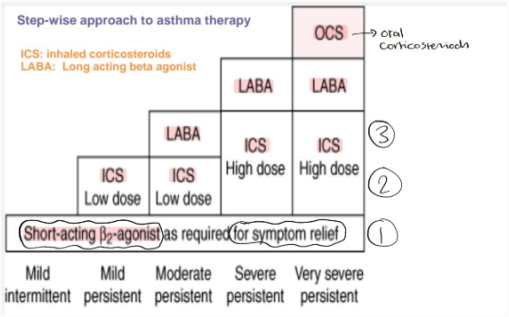
✓ Cough - usually in spasms & to the point of vomiting - **night-time worse than day-time**.
✓ Cough may follow exposure to cold air, exercise,
URTI (common cold), or exposure to an allergen.
✓ **Dyspnea** > cough or wheezing > sputum.
✓ Past history of bronchiolitis as a child.
✓ Family history of asthma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

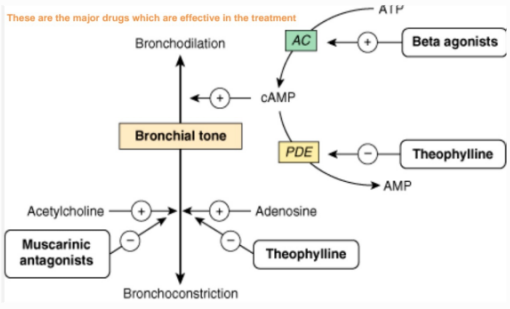
Index of Severity

	Peak Expiratory Flow Rate % Predicted	Peak Expiratory Flow Rate variability Lability (%) (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

- Objective Diagnosis of Asthma:

• Reduced FEV1 & FEV1/FVC ratio (spirometry).
• Reduced Peak Expiratory Flow Rate (FEFR).
• Reversibility with Bronchodilators بخاخات.
• Heightened response to Methacholine Test.
• Increase in expired Nitric Oxide. (NO = inflam.).
• Increase in Inflammatory mediators and their metabolic products in body fluids.





- Overview 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 Corticosteroids, Cromolyn, Ipratropium
1990's:
Inhaled Corticosteroids, Beta-agonists, Theophylline, Leukotriene Inhibitors
2000's:
Corticosteroids + LABA, LTRAs, Theophylline, Cromolyn, Ipratropium, Tiotropium
2010's:
Prevention including gene therapy.

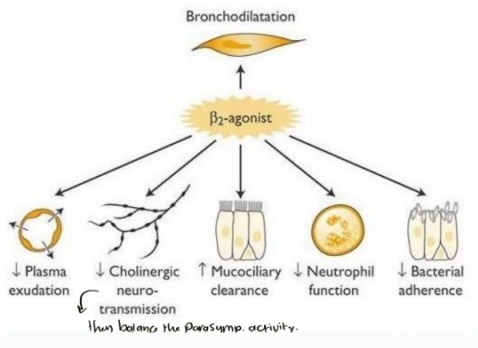
- Relievers / Controllers: رح ينشرح عنهم واحد واحد لقدام

• Quick relief medications:
1) Inhaled Short acting Beta-2 Agonists.
2) Inhaled Anti-cholinergics.
3) Systemic Corticosteroids.

• Long-term control medications:
1) Topical (inhaled) Corticosteroids.
2) Inhaled Cromolyn Na & Nedocromil.
3) Oral Methylxanthines (Theophyllines).
4) Inhaled Long-acting Beta-2 Agonists (LABA).
5) Oral Leukotriene modifiers (LTRA).

- Beta 2-Adrenergic Agonists roles:

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



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

- Molecular Actions:

- Increase cAMP.
- Activate protein kinase A.
- Phosphorylate kinases.
- All lead to decreased cytosolic Ca++ thus ⬇️ muscle contraction.

- B2-selective drugs:

1) **Isoproterenol** (B1 & B2).
2) **Terbutaline** (B2 selective).
3) **Metaproterenol** (B2 selective).
4) **Albuterol** (B2 selective).
5) **Salmeterol** (B2 selective).

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

- Beta 2-Adrenergic Agonists:

- Epinephrine:

- Obtained from bovine adrenal gland.
- Stimulates **α, β1 & β2** receptors.
- **Not effective orally**.
- **Subcutaneous**.
- **MOA:**

It raises Bp ➡️ B.D.

- **Uses:**

1) **Emergency (status asthmaticus).**
2) **Anaphylactic shock.**

- Isopreterenol:

- Stimulates **β1 & β2** receptors.
- First (1960s) **convenient, pocket- sized** multidose **inhalers**.
- Considerable **tachycardia & pounding** خفقان.

Release of histamine → V.D

Epinephrine → V.C → a physiological (Not pharmcological) antagonist.

لأنه ما بيشتغل عال Histamine receptors

بيشتغل عال Receptors تبعته اللي هي ال α و ال β (B2)

Short acting Beta 2-Adrenergic Agonists:

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

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

Long -acting Beta 2-Adrenergic Agonists(LABA)

- inhaled bronchodilators:**12 hours**.
- Suppress **night-time attacks**.
- Controllers **with steroids**.
- **No tachyphylaxis**.

- Salmeterol.
- Formoterol.

- TOXICITY:

بسبب وجود ال B_rec. بالرئة تتأثر بال high doses..

- **Nervousness, Anxiety, Tremor**.
- Due to vasodilation, may **increase perfusion** of poorly ventilated lung units and might transiently **decrease PaO2**.
- **Tachyphylaxis** (tolerance).
- Increased mortality due to **cardiac toxicity, Because the are B2 selective not specific**.

- 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 & more frequently in blacks) **deteriorated with regular use of albuterol or salmeterol**.

There is a heterogenicity in responding to drugs :المغزى

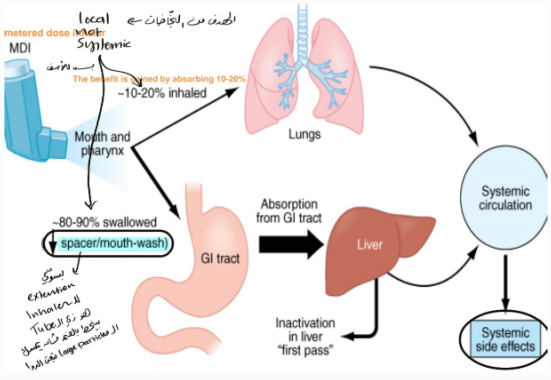
- "A Nested Case-Control of the Relation Between Beta-Agonists & Death and Near Death From Asthma"
  - All deaths & Beta agonist use were studied for 1 year.
  - As Beta Agonist use increased, risk of death increases.
  - For each canister per month increase in use, the risk of death doubled.

B-agonists الكحول
death اكثر بسبّوا
بسبب ال
Cardiac
" Stimulation

Conclusion:

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

(مرّات الsteroids بكونوا أحسن منهم!)



- Problems of Metered Dose Inhalers (MDI):
  - Cap not removed prior to use.
  - Timing of canister actuation to inspiration is critical (only first air in gets to the right place).
  - Inspiration too rapid is wrong, it should take 4-5 seconds
  - Nasal inspiration contains no medication
  - Spacers not used

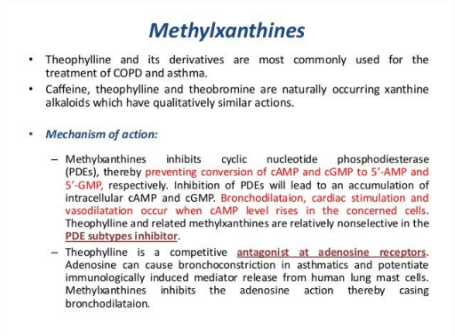
- Spacer:

- A large volume chamber attached to a MDI, used to decrease drug deposition in 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**.

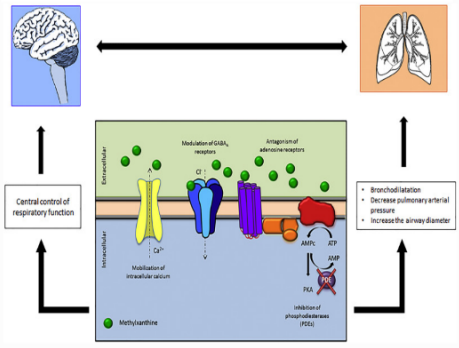
"يؤمن لدرجة أنه عندما يذهب إلى الحقل
ليسأل الله المطر، يأخذ معه مظلّة ومعطفا
جلديا لكي لا يبلّله المطر في طريق العودة.."

LEC 3:

- Methylxanthines: (actually came before B2 selective agonists).
- Xanthine derivatives are found in tea & coffee.



- **Theophylline**.
- **Aminophylline**.
- Were the mainstay treatment (60s-70s).
- Oral and Intravenous.
- CNS stimulants
- **SE:** Cardiovascular stimulants; arrhythmias (sinus tachcardias). Nausea, GIT irritation, diarrhea.
- **MAO**:
- Phosphodiesterase inhibition. (PDE inhibits cAMP cleavage).
⬆️cAMP = smooth muscles dilation & relaxation.
- Adenosine receptor stimulation.
- Anti-inflammatory activity.



- **Problems**:
- Optimal dosing is very difficult (because of low therapeutic index)
- Wide inter-individual variation in the rate of hepatic metabolism.
- Half life: 3-16 hours.
- Food & drug interactions (erythromycins and ciprofloxacin).

So needs monitoring.

- 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)** & **airway inflammatory infiltration**.

- Anticholinergic Agents: (anti-parasymp. ➡️ B.D.)
- **Atropine**:
- Can be inhaled, but; can cause **systemic** side effects.
- Impairs mucociliary clearance leading to dryness, and consequently, impaired clearance of airway secretions.
- **Ipratropium Bromide Inhaler**:
- **Poorly absorbed** from respiratory mucosa.
- Does not impair clearance of airway secretions.
- Causes minimal cardiac or central effects.
- Metered dose inhaler (MDI) & as a solution for nebulization تبخيرة.
- **Mainly for COPD**, **not for asthma**, because of slow onset (10-15 minutes) -so **not** for emergency- & low potency.
- Might be very useful in special conditions (**beta blocker-induced asthma**, resistant attacks, cardiac patients)

B-agonist ما بنفع بعطيهم ←
مريض الـ BB بعطي لمرض
القلب ما بنفع بعالجهم
Cardiac stimulation.
(B-receptors لازم بعطيهم دوا تابع ما بيشتغل على الـ)

- Anti-inflammatory Agents & Alternative Therapy:

1- Coricosteroids.
2- Inhibitors of Mast Cell Degranulation.
3- Leukotriene Pathway Modifiers.
4- Immunomodulatory Agents.

1- Coricosteroids:

• Inhibit the synthesis & release of many chemical mediators (histamine, PGs & cytokines).
• Suppress the inflammatory cell influx & 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.

- **MAO:** intra-nuclear:
- 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.
- **Short term systemic use in severe refractory attacks.**
- **Long term use for "Steroid Dependant" asthma**. (They stay on low doses for long time).
- **Systemic Use**: إيقاف الـ Steroids بيجيبلهم الأعراض

1) Oral or injectable (**Cortisone, Prednisolone, Dexamethasone**)
2) Inhalation: Aerosol treatment is the most effective way to avoid the systemic adverse effects (**Beclomethasone, Triamcinolone, Flunisolide, Budesonide, Fluticasone**).

- **Local Side Effects**:
Hoarseness of voice (dysphonia), sore throat & cough. → الكل إعطاء المريض B_2-agonist قبل الـ corticosteroid.
Candida infection.

- **Systemic Side Effects**: (in high doses)
Osteoporosis, cataract, glaucoma, growth retardation, adrenal suppression, CNS effects and behavioral disturbances, increased susceptibility to infections, and teratogenicity.

→ طا يوقف العلاج فجأة

السبب إنه طا ياخد Large doses لفترة طويلة بتصير تثبط الـ ACTH adrenocorticotropic hormone

فلما يوقف الدوا فجأة والـ ACTH لسة نايم (ما بيشتغل بسرعة) ← Acute Adrenal insufficiency (Suppression) Adrenal

ACTH الـ Responsive بتشتغل

2- Inhibitors of Mast Cell Degranulation:

- Cromolyn Na & 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. → !! Histamine لـ إنتاج بعد ما بيشتغل
- 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. (Cuz NO MAST CELLS).

3- 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**), & does not involve IgE antibody response. → Not Ag-ab interaction it is due to shunting.
- 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.

A- Inhibitors of 5-Lipoxygenase enzyme:

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

B- Antagonists of Cysteinyl Leukotriene Receptors:

- Montelukast.

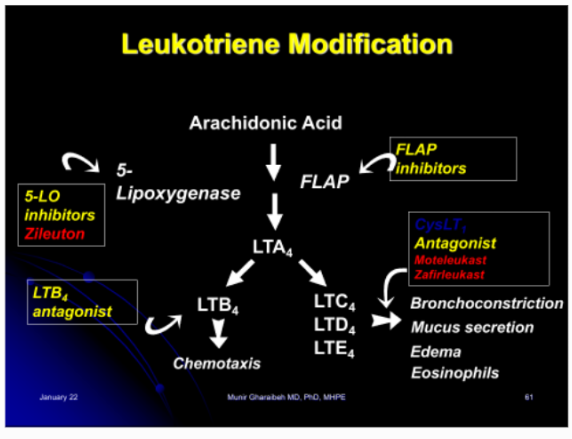
- Zafirlukast.

Some patients improve, others do not and may develop:

Churg Strauss Syndrome:

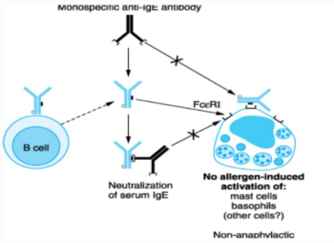
- Rare reaction in newly treated asthmatic patients.
- **Severe** inflammatory rxn, pulmonary infiltration, neuropathy, skin rash, & cardiomyopathy.
- A common finding is systemic vasculitis with eosinophilic infiltration and granuloma formation.
- Could also be due to unmasking of vasculitis after steroid withdrawal.

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



- Montelukast - Beta agonist combination / a study:
⬇️ percent of patients needing systemic use of corticosteroids by 39%.
⬇️ in night-time awakenings.
⬇️ percent of patients having asthma attacks by 37%.
⬇️ need for beta-agonists by 21%.

لأنه في كثير مرضى مابيتحملوا الـ Steroids لأنه immunosuppressor



4- Immunomodulatory Agents (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.
- 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:

Remember that asthma = B.C, exudation → (Dehydration), Inflammation. لازم نعالجهم الثلاث.

- 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) and, if confirmed, would stimulate the development of new diagnostic methods and antimicrobial therapies.
- Feeding **Lactobacillus caseii (probiotic موجود باللبن)** to infants born to allergic parents reduced the rate of allergic dermatitis at age 2 years, offers reason for hope.

هاداكاي أشوه بال Allergic dermititis بالأطفال، مش بال Bronchial asthma

- 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.
- **Treatment:**
- **Oxygen.**
- **Inhaled short-acting β2 agonists.**
- **Oral or Parenteral corticosteroids.**

- Subcutaneous β2 agonists.
- Inhaled ipratropium maybe effective in some patients.
- Epinephrin by subcutaneous injection.
↳ used in anaphylactic shock as a life-saving treatment.

- 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. → زي البخاخات والبخيرات (nebulizers)
- Even more immediate beta-agonist therapy via an "Epi-pen" is readily available. ↳ like epinephrine

- 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 & drugs in rational combinations.

LEC 4: TB TREATMENT:

Drug Treatment of Tuberculosis

- There are about 9 million new cases annually.
- TB killed 1.7 million people worldwide in 2006.
- Antituberculous Agents:

A) Primary or First Line Drugs: (RIPE)

Rifampin "Rifadin" or "Rimactane"

Isoniazid (INH)

Pyrazinamide

Ethambutal

Streptomycin

Recommended Duration of Therapy

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

1) Isoniazid (INH):

- Most active.
- Small molecule, water soluble,
- Structurally related to Pyridoxine.
- Prodrug, activated by KatG, the mycobacterial catalase-peroxidase,
- Blocks **mycolic acid** synthesis, and consequently mycobacterial cell wall synthesis, leading to a bactericidal effect in growing TB cells.
- TB lesion contains more than 108 bacilli
- When used alone, resistance is 1 in 106.
- A lesion usually contains 108 cells.
- When used in combination, the probability of resistance will be 1 in 10 6 * 10 6 =1012.
- Readily absorbed
- Widely distributed, penetrates into macrophages.
- Metabolized by acetylation: – Slow and Fast Acetylators.
- SE:
- **Hepatitis**: in about 1%, Anorexia, N,V, jaundice, pain, death. Depends on age, alcohol, pregnancy
- **Neuropathy**:10-20%

More in slow acetylators, malnutrition, alcoholism, DM, AIDS, uremia.
Due to pyridoxine (vit B6) defeciency. (INH promotes pyridoxine excretion).

- **Neurotoxicity**: Memory loss, Psychosis, Seizures.
- **Hematologic, Tinnitus, GIT, drug interactions.**

2) Rifampin:

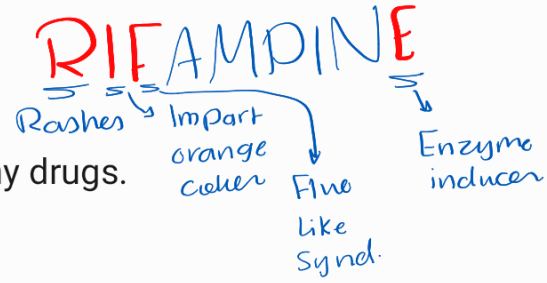
- Stretomyces miditerranei.
- Gram+ve and –ve
- Mycobacteria, enterococci and chlamydia.
- Binds to the beta subunit of bacterial RNA polymerase and therefore inhibits RNA synthesis.
- Bactericidal

- Well absorbed, highly bound to proteins.
- Widely distributed.
- Hepatic metabolism and exhibits enterohepatic recirculation.
- **Uses:**
- TB
- Leprosy
- Meningococcal (N. Meningitidis) **Carrier** State.
- **Prophylaxis** in H.influenzae.
- Serious Staph osteomyelitis & valve endocarditis.

valve endocarditis It is an inflammation of the inner tissues of the heart, the endocardium, usually of the valves. It is caused by infectious agents, or pathogens, which are largely bacterial

Osteomyelitis (OM) is an infection of bone.[1] Symptoms may include pain in a specific bone with overlying redness, fever, and weakness.[1] The long bones of the arms and legs are most commonly involved in children while the feet, spine, and hips are most commonly involved in adults

- **Toxicity:**
- Imparts harmless orange color to secretions (tears, urine, sweat).
- Rashes.
- Hepatitis.
- Flu-like syndrome.
- Liver Enzyme Inducer, so can lower serum levels of many drugs.



3) Streptomycin:

- Primary---Second-line----- Primary anti-tuberculus agent.
- Plague, Tuleremia حمى الأرانب , Brucellosis الحمى المالطية
- Endocarditis.
- **Toxic:**
- Allergy: Fever, Rashes
- Pain, after intramuscular injection.
- Irreversible vestibular toxicity (Hearing loss).
- Nephrotoxicity.

Tularemia is an infectious disease caused by the bacterium Francisella tularensis. Symptoms may include fever, skin ulcer, and large lymph nodes

B) Secondary or Second Line Drugs:

Ethionamide
Capreomycin
Cycloserine
Para-Amino-Salicylic Acid (PAS)
Amikacin
Flouroquinolones
Linezolid
Rifabutin

Ethiopian PAS Cap Amikacin on the flour of lineolid Rifabutin Cycloserine أجن وظفته

إثيوبي بس كب كاسة طحين على أرض البيت الريفي للحجة ليلى ولبنى .. سريلي أجنت وظفته

- Indications for Secondary or Second Line Drugs:

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

Ethionamide:

- Related to Isoniazid.
- Blocks mycolic acid synthesis.
- Oral, Good distribution.
- **SE:** Poorly tolerated:
- Severe GIT irritation.
- Neurotoxic.
- Hepatotoxic.

Capreomycin:

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

Cycloserine:

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

Para-Amino-Salicylic Acid (PAS):

- Folate synthesis antagonist
- Well absorbed
- Dose 8-12 gm/day
- Widely distributed, except CNS
- Excreted in urine.
- GI toxicity
- Hypersensitivity reactions
- Crystalluria

Amikacin:

- Multi-drug-resistant strains
- Atypical mycobacteria

Flouroquinolones:

- Are an important addition
- Resistance develops rapidly if used alone.

Linezolid:

- Multidrug-resistant strains.
- Bone marrow suppression
- Irreversible peripheral & optic neuropathy.
- Drug of last resort الحل الأخير

Rifabutin Rifapentine:

- Related to Rifampin.
- Inhibit bacterial RNA polymerase.
- Both, like Rifampin, are inducers for CYP P450 enzymes. But Rifabutin is less potent inducer.
- Rifabutin is indicated in place of Rifampin in the treatment of **TB in HIV-infected patients receiving protease inhibitor or non-nucleoside reverse transcriptase inhibitor** (e.g. efavirenz)

- Annually, 9 million cases are recorded.
- 5% of these are drug-resistant tuberculosis.
- Forty-nine percent of those with XDRTB died compared to 19 percent of patients with ordinary MDR-TB,

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)