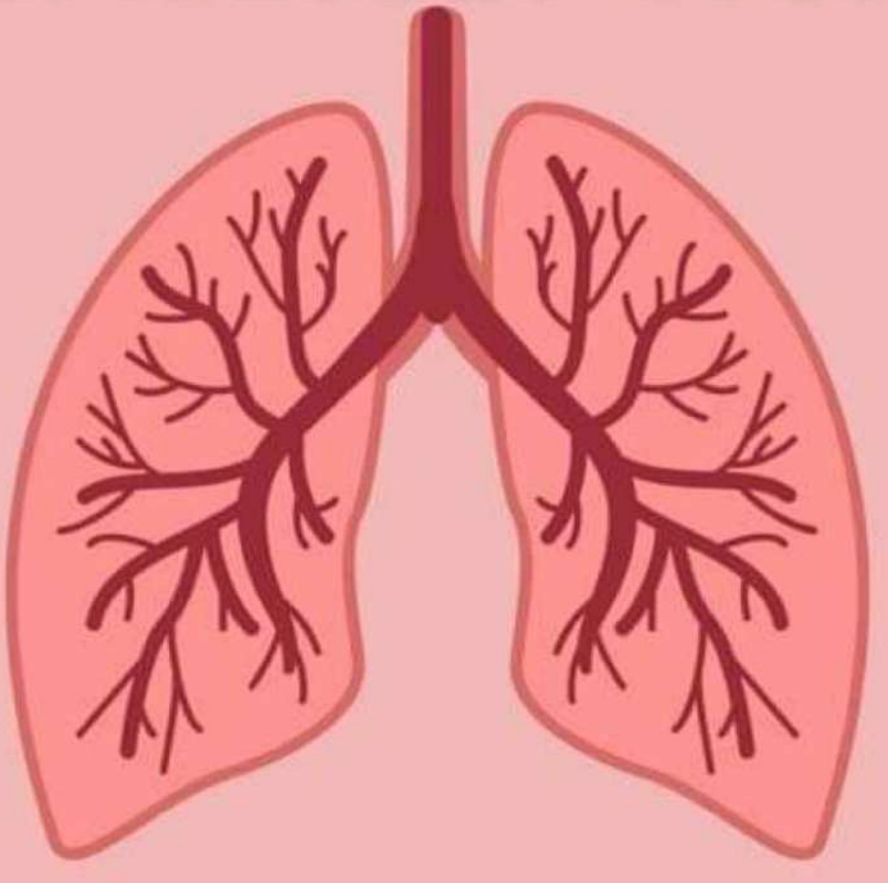
النادي الطبي

RESPIRATORY SYSTEM



SUBJECT : Pharmacology

LECTURE : 2

DONE BY : Johainah Taha

Lectures 2-3: Treatment of Asthma

Respiratory system
Second year
Medical school
Hashemite University
2^{nd} semester 22/23
Sofian Al Shboul, MD, PhD.

فيديوهات استفدت منها :

www.youtube.com › watch
Respiratory Pharmacology (Ar) - Therapy of bronchial asthma

Chapter 07: Respiratory PharmacologyGoogle Play link to Android App:https://play.google.com/store/apps/details?...
YouTube · Clinical Pharmacology Lectures · Feb 14, 2017

رهيب ♡

احضروه 's Break ☺ واعملولنا like

Overview & definition

❖A chronic inflammatory disease characterized by variable and reversible airflow obstruction, and easily triggered bronchospasms by hyperresponsive airways inhaled stimuli.

الفرق بينه و بين COPD انه reversible و لكن بسبب انه chronic فما اله curable treatment

❖Incurable, but most people can control their symptoms.

❖Majority of kids with asthma eventually grow out of it.

لو كان في طفل معاه asthma بستناه ليكبر و يصير بال teen-age لأنه ممكن تختفي ال asthma منه

Asthma is charaterized by episodes of acute bronchoconstriction that cause shortness of breath, cough, chest tightness, wheezing, and rapid respiration.

Risk factors & triggers

*ال family history كمان شي بميز ال asthma عن COPD

*ال smoking ما بسبب asthma بس بعمل asthma attack

Risk factors & triggers

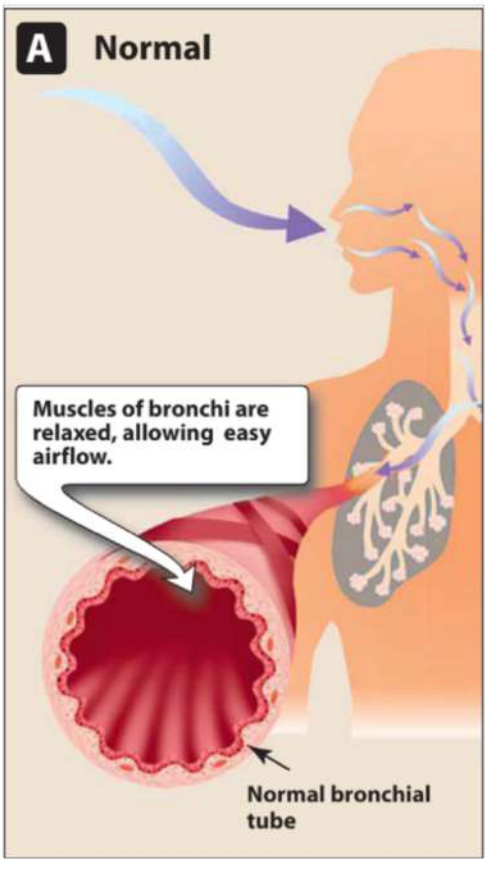
- Family history is a risk factor for asthma.

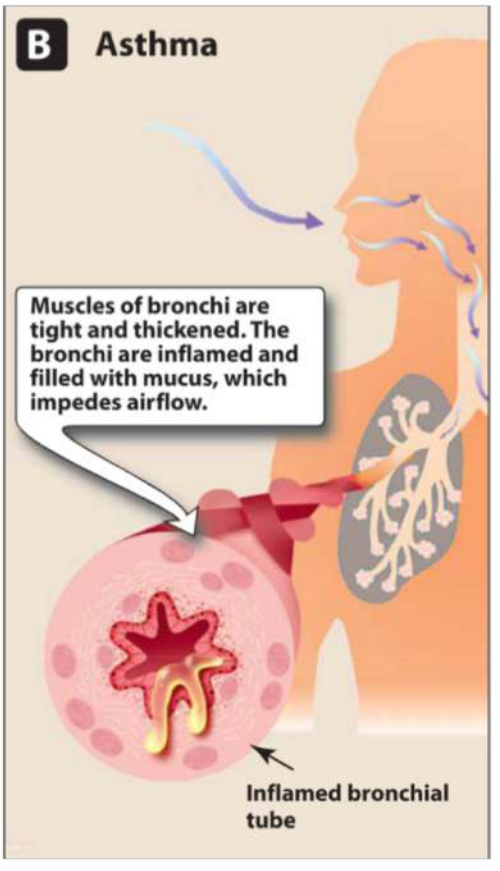
الدليل

- If one identical twin is affected, the probability of the other having the disease is approximately 25%.

- >100 genes had been associated with asthma such as **IL10**, **CTLA4**, **IL4R** and ADAM33.

بنلاحظ انه في اكثر من جين مسؤول عن asthma هدول الجينات immune related
لهيك صعب اعمل الهم inhibition و بنفس الوقت كثار





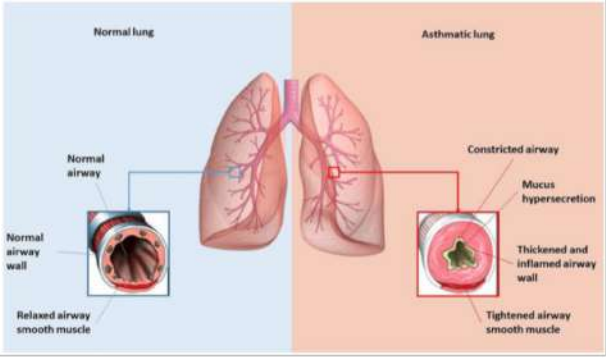
Pathophysiology

Contraction of bronchial smooth muscle
bronchial wall inflammation
increased secretion of mucus

bronchoconstriction and airflow obstruction.

COPD is progressive

Asthma is usually not a progressive disease. However, if untreated, asthma may cause airway remodeling, resulting in increased severity and incidence of asthma exacerbations and/or death.



The underlying inflammation of the airways contributes to airway hyper-responsiveness, airflow limitation, respiratory symptoms, and diseasechronicity.

Asthma attacks may be triggered by exposure to allergens, exercise, stress, and respiratory infections.

Unlike COPD, cystic fibrosis, and bronchiectasis, asthma is usually not a progressive disease.

COPD is progressive, which means it gets worse over time. Asthma is a reversible condition when the right treatment is received at the right time. This makes early treatment important, especially when ACOS occurs.

Asthma COPD overlap Syndrom

هي حنحكي عنه كمان شوي

كل يوم ممكن يكون بداية

منا فودة

* الـ factors اللي حكينالهم فوق بيعملوا (dust, smoking, cold air)

chronic irritation ← inflamation ← immune reaction

Releases inflamatory mediators ← infiltration to immune cells

حتزيد الطين بلة ← (ex) B-Cells, T-Cells, Mast cells, neutrophiles

(ex) 1. Histamine 2. Seretonin 3. PGD 4. PGF2α 5. LTs(B4 6. PHF 7. IL 2, 5, 9...

وغيرهم كتير

وهنا المشكلة بالـ Asthma ، انا كارزة أقفل ايه وقايه !؟

* and these mediators Cause → smooth muscle → Constriction / hypertrophy (تبقى أتزيد على حساب lumen)

→ Bronchial gland → ↑ Secretions

→ Vessels → Vasodilation → capillary leaking → edema → narrowing

بالعلاج لازم أعطي نوع شي non-specific anti-inflamatory drug

← ليقدر يغطي كل mediators

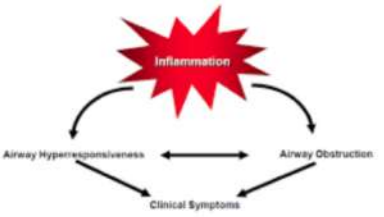
* وأفضل مثال : Cortisol

ثانياً : بدي أعطي شي بيخلصني من Spasm ويعمل dilation.

Pathophysiology & pathogenesis

- Asthma pathophysiology components:

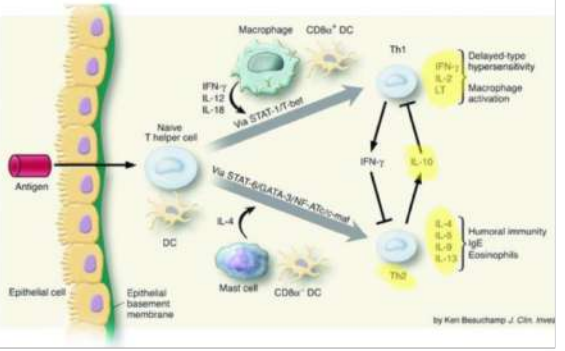
1. Airway inflammation
2. Intermittent airflow obstruction
3. hyperplasia of the cells of all structural elements of the airway wall.



- Several immune cells are implicated:

1. Eosinophils and CD4+
2. Mast cells
3. Th2 lymphocytes
4. Basophils

مهم مهم

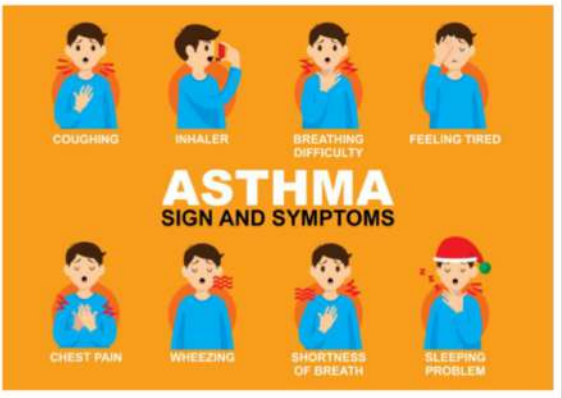


- Foreign materials (allergens)>> ↑ **IgE** (genetically determined)>> IgE antibodies bind to mast cells in the airway mucosa

Signs & symptoms

مهمين للcase لنعرف عن اي مرض عم نحكي

- Wheezing (could be absent during most severe episode)
- Shortness of breath
- Chest tightness
- Coughing



- Symptoms are usually worse at night and in the early morning or in response to exercise or cold air.

خلي ببالكم انه الattack من الasthma اقل من COPD

Asthma vs COPD

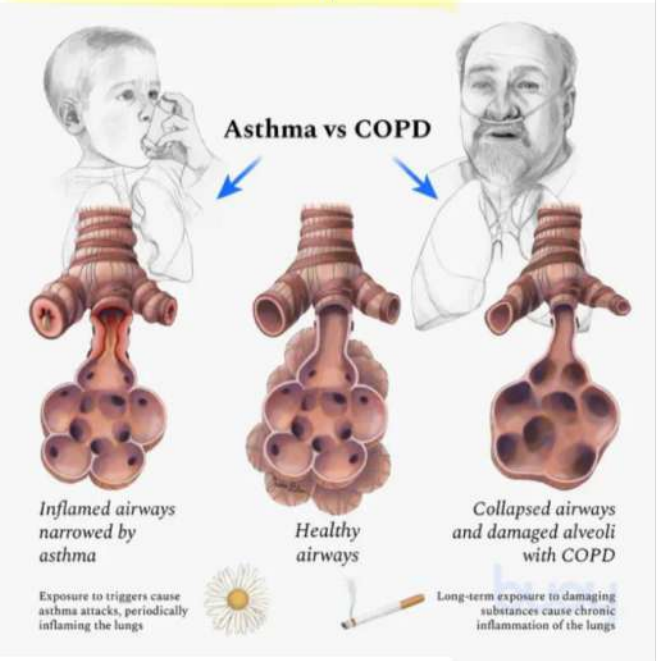
- Asthma is not considered as a part of COPD because:

1. Airway obstruction in asthma is usually **reversible** (if left untreated, it can become irreversible
2. Asthma affects the **bronchi** (emphysema effect the alveoli)

- Asthma + component of irreversible airways obstruction = the asthma-chronic obstructive disease (COPD) overlap syndrome (ACOS).
- people with ACOS exhibit increased morbidity, mortality and possibly more comorbidities

يعرضن
اعراض
ومنيات
لو الأمراض المصاحبة

ACOS: Asthma COPD overlap syndrom

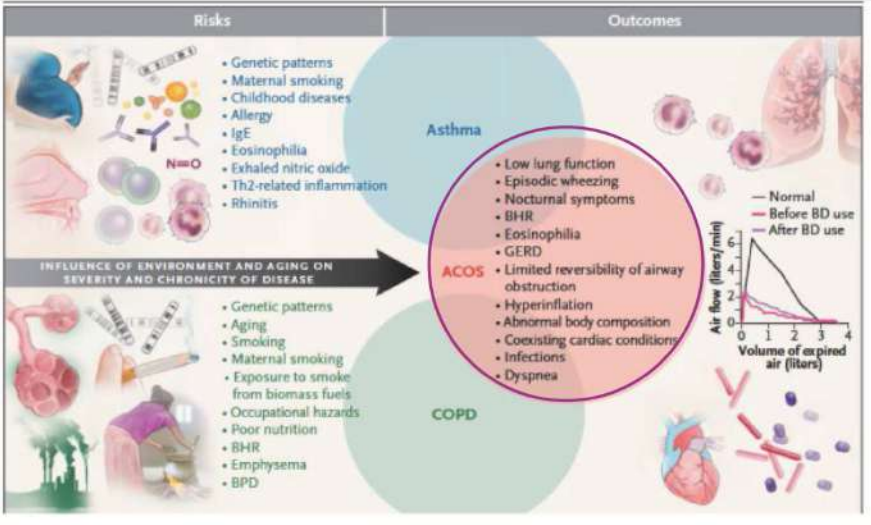


- Compared to asthma, COPD occurs in **older** patients, is associated with **neutrophilic** rather than eosinophilic inflammation, is **poorly responsive** even to high-dose inhaled corticosteroid therapy, and is associated with **progressive, inexorable loss of** pulmonary function over time, especially with continued cigarette smoking.

حتمي

	Asthma	COPD
Age of onset	Usually < 40 years	Usually > 40 years
Smoking history	Not causal	Usually > 10 pack-years
Sputum production	Infrequent	Often
Allergies	Often	Infrequent
Disease course	Stable (with exacerbations)	Progressive worsening (with exacerbations)
Spirometry	Often normalizes	Never normalizes
Clinical symptoms	Intermittent and variable	Persistent

Asthma-COPD overlap syndrome (ACOS) is diagnosed when you have symptoms of both asthma and COPD. ACOS is not a separate disease, but rather a way for doctors to recognize the mix of symptoms and select a treatment plan that is most appropriate for you.



Interplay of asthma and COPD-related risk factors in ACO - Postma and Rabe NEJM 2015

صورة من النت
بتوضح تداخل المرضين

أكثر بيختلف عن COPD

Asthma management

- Identifying triggers (محفزات) and eliminating exposure to them is considered the most effective treatment

مثلا لو كان ال trigger هو بسة لازم نعمل elimination الها

- Aims of asthma therapy:

1. Decrease the intensity and frequency of asthma symptoms
2. Prevent future exacerbations
3. Minimize limitations in activity related to asthma symptoms

كل مرضى ال asthma بتضايقوا من الدخان لهيك ما بصيروا يقربوا من اي مكان فيه تدخين

- Medications for asthma are broadly classified into fast-short-acting (1) and long-acting (2) categories

Asthma classification

	Intermittent	Persistent Asthma: Mild	Persistent Asthma: Moderate	Persistent Asthma: Severe
1 Symptoms	≤2 days/week	≤2 days/week but not daily	Daily	Throughout the day
2 Night Awakenings	≤2 days/month	3-4 times/month	>1 time/week but not nightly	Often 7 times/week
3 Use of SABAs (not for EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
4 Interference w/ Normal activity	None	Minor limitation	Some limitation	Extremely limitated
5 Lung Function	FEV_1>80% predicted FEV_1/FVC normal	FEV_1≥80% predicted FEV_1/FVC normal	FEV_1=60-80% predicted FEV_1/FVC reduced 5%	FEV_1<60% predicted FEV_1/FVC reduced >5%
Recommend Step for Initiating Treatment	Step 1	Step 2	Step 3	Steps 4 - 6

Severity of Symptoms →

EIB: Exercise induced bronchoconstriction
FEV1: forced expiratory volume in one second
FVC: forced vital capacity
SABA: short-acting beta-2 agonists.

اول خطوة لمعرفة العلاج المناسب للمريض هي التشخيص
و بعد ما اشخص المريض لازم اصنفه و اعمل اله classification بتصنيف بتكون من 5 variables

توضيح الclassification :
#النقطة الاولى بشوف الاعراض الي حكينا عنهم بالسلايدات الماضية كم مرة بتظهر عليهم بالأسبوع

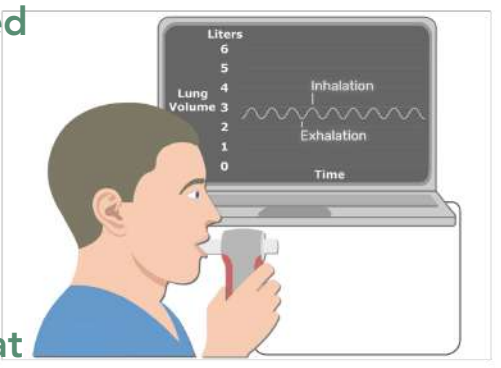
#ثانياً بشوف كم مرة المريض صحي و هو نايم بسبب الشعور بضيق النفس؛ طبعا كل ما زادت مرات الاستيقاظ كل ما كان الوضع اسوأ، ركزوا لو كان العدد بالشهر او بالاسبوع

#ثالثاً بشوف عدد مرات استعمال الSABA و هو عبارة عن بخاخ، كثرة استعماله و الاعتماد عليه و الoveruse اله ابدا مو منيحة لانه بزيد الmortality

#رابعاً هل الasthma متداخلة و عم تأثر على نشاطات الانسان الطبيعية مثل الشهيق و الزفير، النوم، و كثير شغلات

#خامساً بشيك عالlung function، حأشرح شوية فسيو :

The FEV1/FVC is a ratio that reflects the amount of air you can forcefully exhale from your lungs. It's measured by spirometry, a test used to evaluate lung function.



It's made up of two measurements:
FEV1: Forced expiratory volume in one second, or the volume of breath exhaled with effort in one second
FVC: Forced vital capacity, or the full amount of air that can be exhaled with effort in a complete breath

FEV1/FVC ratio helps identify the type of condition you have and whether it is restrictive or obstructive.
Restrictive lung diseases (such as pulmonary fibrosis) affect your ability to inhale.
Obstructive conditions (such as asthma and COPD) affect your ability to exhale.
This test is often used to monitor lung disease, especially if you have an obstructive condition such as asthma.
Normal =80%
Decreased FVC With Normal FEV1/FVC Ratio = Restrictive lung disease
Decreased FEV1/FVC Ratio = Obstructive ling disease

* All patients with asthma should have immediate access to an inhaled bronchodilator with a rapid onset of action for prompt relief of asthma symptoms, SABA: albuterol or levalbuterol)

Asthma management

مهمين كتير وعليهم سؤال بالامتحان

- **Step 1:** SABA as needed (preferred) OR Low-dose ICS + Long- (fast) acting beta agonist (budesonide-formoterol or budesonide-albuterol) as needed
- **Step 2:** Low-dose ICS daily and separate SABA as reliever (preferred) OR Step 1 Low-dose ICS + long-(fast) acting beta agonist as needed OR leukotriene receptor antagonist (LTRA) daily with SABA as needed
- **Step 3:** Low-dose ICS-formoterol OR Low-dose ICS-LABA combination inhaler daily and separate SABA as reliever.
- **Step 4-6:** Medium-to high-dose ICS-LABA combination inhaler daily and separate SABA as reliever plus LAMA daily

بدكم رأيي ؟ ارجعوا للسلايد بعد ما تدرسوا عن الأدوية 👍🏻
و حأضيفها بعد ما نخلص المحاضرة

Agents used for Asthma

حفظ ← نتنبه انه موكلم بعالجوا Asthma

MEDICATION	IND
SHORT-ACTING β_2 ADRENERGIC AGONISTS (SABAs)	
Albuterol PROAIR, PROVENTIL, VENTOLIN	Asthma, COPD
Levalbuterol XOPENEX	Asthma, COPD
LONG-ACTING β_2 ADRENERGIC AGONISTS (LABAs)	
Arformoterol BROVANA	COPD
Formoterol FORADIL, PERFOROMIST	Asthma, COPD
Indacaterol ARCAPTA	COPD
Olodaterol STRIVERDI RESPIMAT	COPD
Salmeterol SEREVENT	Asthma, COPD
INHALED CORTICOSTEROIDS	
Beclomethasone BECONASE AQ*, QVAR	Allergic rhinitis, Asthma, COPD
Budesonide PULMICORT, RHINOCORT*	Allergic rhinitis, Asthma, COPD
Ciclesonide ALVESCO, OMNARIS*, ZETONNA*	Allergic rhinitis, Asthma
Fluticasone FLONASE*, FLOVENT	Allergic rhinitis, Asthma, COPD
Mometasone ASMANEX, NASONEX*	Allergic rhinitis, Asthma
Triamcinolone NASACORT*	Allergic rhinitis, Asthma

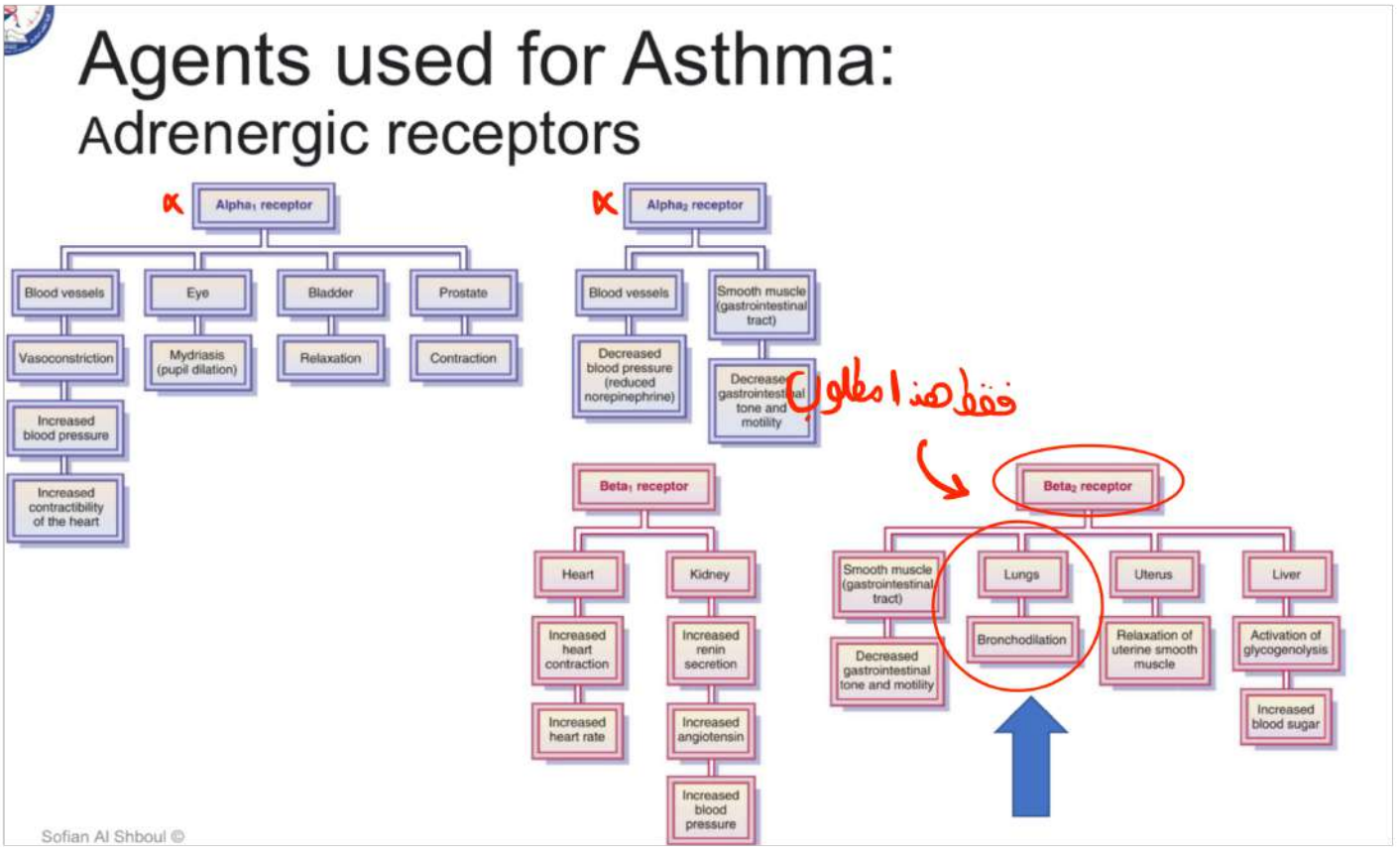
LONG-ACTING β_2 ADRENERGIC AGONIST/CORTICOSTEROID COMBINATION	
Formoterol/budesonide SYMBICORT	Asthma, COPD
Formoterol/mometasone DULERA	Asthma, COPD
Salmeterol/fluticasone ADVAIR	Asthma, COPD
Vilanterol/fluticasone BREO ELLIPTA	COPD
SHORT-ACTING ANTICHOLINERGIC	
Ipratropium ATROVENT	Allergic rhinitis, Asthma, COPD
SHORT-ACTING β2 AGONIST/SHORT-ACTING ANTICHOLINERGIC COMBINATION	
Albuterol/ipratropium COMBIVENT RESPIMAT, DUONEB	COPD
LONG-ACTING ANTICHOLINERGIC (LAMA)	
Aclidinium TUDORZA PRESSAIR	COPD
Glycopyrrolate SEEBRI NEOHALER	COPD
Tiotropium SPIRIVA	Asthma, COPD
Umeclidinium INCRUSE ELLIPTA	COPD
LABA/LAMA COMBINATION	
Formoterol/glycopyrrolate BEVESPI AEROSPHERE	COPD
Indacaterol/glycopyrrolate UTIBRON NEOHALER	COPD
Vilanterol/umeclidinium ANORO ELLIPTA	COPD
Olodaterol/tiotropium STIOLTO RESPIMAT	COPD

OTHER AGENTS	
Roflumilast DALIRESP	COPD
Theophylline ELIXOPHYLLIN, THEO-24	Asthma, COPD

The most important 2 drugs to give to Asthma patients:-

(1) Bronchodilator
- β2 - agonist
- muscarenic blockers (M3)
- Methylxan

(2) Anti - inflamatory drug.



An adrenergic agonist is a drug that stimulates a response from the adrenergic receptors. The five main categories of adrenergic receptors are: α1, α2, β1, β2, and β3

Stimulation of beta-2 receptors in the lungs causes bronchodilation
و أساساً شغلي بالasthma حيكون على B2

Agents used for Asthma:
Adrenergic agonists

MEDICATION	
SHORT-ACTING β_2 ADRENERGIC AGONISTS (SABAs)	
Albuterol PROAIR, PROVENTIL, VENTOLIN	Asthma, COPD
Levalbuterol XOPENEX	Asthma, COPD
LONG-ACTING β_2 ADRENERGIC AGONISTS (LABAs)	
Arformoterol BROVANA	COPD
Formoterol FORADIL, PERFOROMIST	Asthma, COPD
Indacaterol ARCAPTA	COPD
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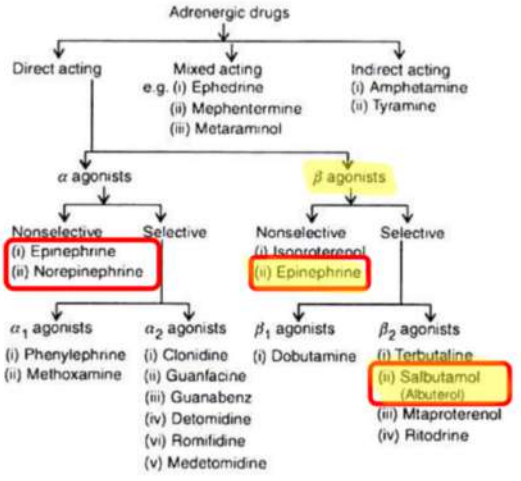
Salmeterol SEREVENT	Asthma, COPD

❖ pharmacological asthma related actions:

1. Relax airway smooth muscle
2. Inhibit release of bronchoconstricting mediators from mast cells
3. Inhibit microvascular leakage (no edema)

❖ **Epinephrine, albuterol, levalbuterol**

Why is epinephrine preferred over norepinephrine for asthma?



epinephrine has a greater effect on beta receptors compared with norepinephrine, norepinephrine binds very poorly to β-2 receptors.

Agents used for Asthma:
Adrenergic agonists (Epinephrine)

- Best delivered by inhalation (greatest effect on airway + least systemic toxicity) ①②
- Effective, rapidly acting bronchodilator when injected SC ① or inhaled as from a pressurized canister ② (لـ مضغوط — علبة بـ)
- International asthma guidelines recommend **against** epinephrine (adrenaline) administration in acute asthma unless associated with anaphylaxis or angio-oedema

مهم جدًا

** انا ما بستخدم الepinphrine الا بحالات الي بتكون severe
وبستخدم مكانه selective beta 2 agonists

Agents used for Asthma:
Adrenergic agonists (Epinephrine)

- Maximal bronchodilation is achieved 15 minutes after inhalation and lasts 60–90 minutes.
- tachycardia, arrhythmias, and worsening of angina pectoris are troublesome adverse effects.
- its use in asthma has been displaced by other, more β2 -selective agents.

Agents used for Asthma:
β2-adrenergic agonists

- Used for quick relief of asthma symptoms, and
- as adjunctive therapy for long-term control of the disease
- SABAs have a rapid onset of action (5 to 30 minutes) and provide relief for 4 to 6 hours.
- Used for symptomatic treatment of bronchospasm
- anti-inflammatory effects?
- Can be used as monotherapy for patients with persistent asthma?

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Salmeterol SEREVENT	Asthma, COPD

*Inhaled Beta 2-adrenergic agonists directly relax airway smooth muscle.

*All patients with asthma should receive a SABA inhaler for use as needed.

*Beta 2 agonists have no anti-inflammatory effects, and they should not be used as monotherapy for patients with persistent asthma.
However, monotherapy with SABAs may be appropriate for patients with mild, intermittent asthma or exercise-induced bronchospasm.
*Direct-acting Beta 2-selective agonists include a/buterol and levalbuterol.

Agents used for Asthma:
β2-adrenergic agonists

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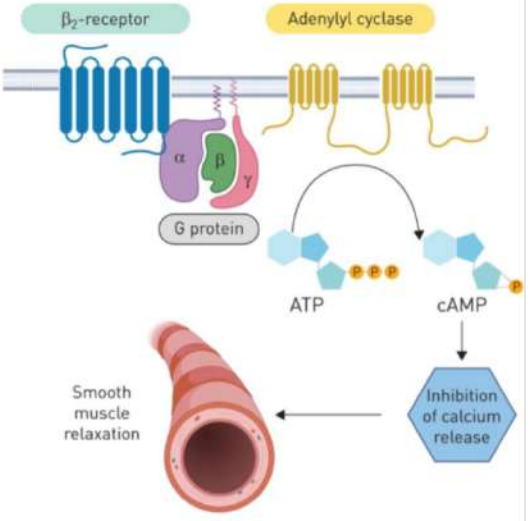
Olodaterol STRIVERDI RESPIMAT	COPD
Salmeterol SEREVENT	Asthma, COPD

- SABAs monotherapy may be appropriate for patients with mild, intermittent asthma or exercise-induced bronchospasm.
- Can be diluted in saline for administration from a hand-held nebulizer but **are no more effective.**
- Nebulized therapy should thus be reserved for patients unable to coordinate inhalation from a metered-dose inhaler

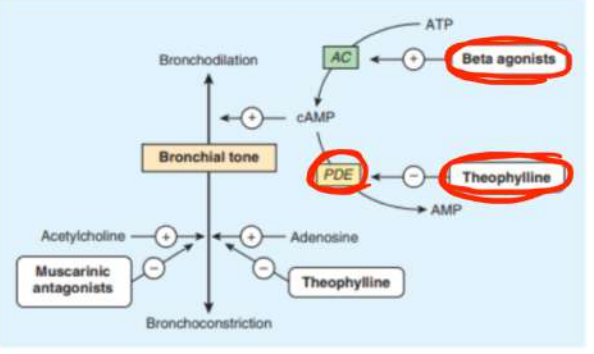


Agents used for Asthma:
β2-adrenergic agonists

- **MOA:** COPD lecture

Receptor activation (G protein (Gs) + adenylyl cyclase) >> **increases intracellular cAMP >> activate protein kinase A (PKA) >>** phosphorylate Gq-coupled receptors >> **reduce intracellular Ca2+ or decrease the sensitivity of Ca2+ >> inhibition of myosin light chain phosphorylation (MLCK) >>** preventing airway smooth muscle contraction.

- Adverse effects: tachycardia, **hyper**glycemia, **hypo**kalemia, **hypo**magnesemia, and skeletal muscle tremors



Agents used for Asthma:
β2-adrenergic agonists

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Salmeterol SEREVENT	Asthma, COPD

- LABAs used in Asthma: salmeterol and formoterol (both are chemical analogs of albuterol).
- longer duration of action, providing bronchodilation for at least 12 hours (because of their high lipid solubility).
- Use of LABA monotherapy is **contraindicated**, and LABAs should be used **only in combination with an asthma controller medication**, such as an inhaled corticosteroid (ICS).

مو لحالهم

Salmeterol Multicenter Asthma Research Trial (SMART) randomized trial comparing salmeterol (MDI) VS placebo. An interim analysis in 26,355 patients found an increase in **respiratory-related deaths and asthma-related deaths**

a drug that has no therapeutic effect.

***ICS remain the long-term controllers of choice in asthma, and LABAs are considered to be useful adjunctive therapy for attaining control in moderate to severe asthma.**

***Although both LABAs are usually used on a scheduled basis to control asthma, adults and adolescents with moderate persistent asthma can use the ICS/formoterol combination for relief of acute symptoms.**

***Adverse effects of LABAs are similar to quick-acting Beta 2 agonists.**

Agents used for Asthma:

Inhaled corticosteroids (ICS)

INHALED CORTICOSTEROIDS	
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Budesonide PULMICORT, RHINOCORT*	Allergic rhinitis, Asthma, COPD
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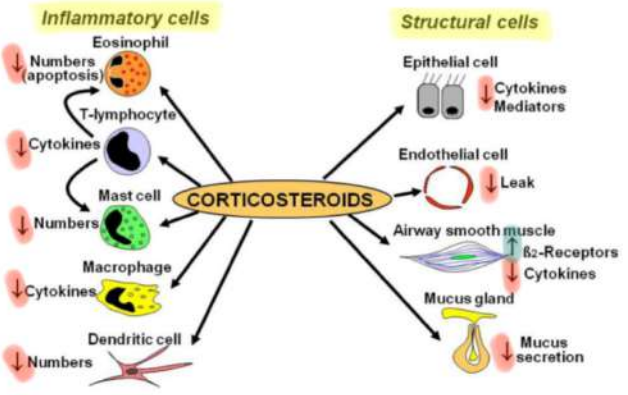
Mometasone ASMANEX, NASONEX*	Allergic rhinitis, Asthma
Triamcinolone NASACORT*	Allergic rhinitis, Asthma

Actions on lung:

- These drugs directly targets underlying airway inflammation:

1. Decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes)
2. Reversing mucosal edema
3. Decreasing the permeability of capillaries
4. Inhibiting the release of leukotrienes.



لـ مهمين عليهم سؤال

They decrease everything except beta 2 receptors.
They are used in Asthma more than COPD.

حل معلومات هذا السلايد مهمة

Agents used for Asthma:

Inhaled corticosteroids (ICS)

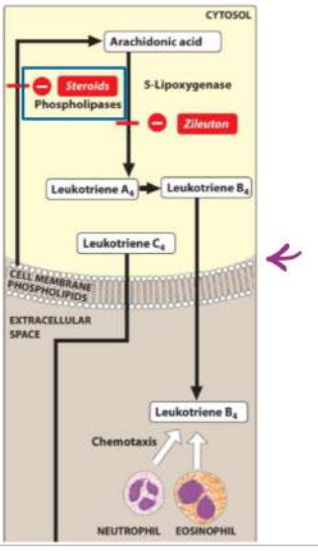
INHALED CORTICOSTEROIDS	
Beclomethasone BECONASE AQ*, QVAR	Allergic rhinitis, Asthma, COPD
Budesonide PULMICORT, RHINOCORT*	Allergic rhinitis, Asthma, COPD
Ciclesonide ALVESCO, OMNARIS*, ZETONNA*	Allergic rhinitis, Asthma
Fluticasone FLONASE*, FLOVENT	Allergic rhinitis, Asthma, COPD
Mometasone ASMANEX, NASONEX*	Allergic rhinitis, Asthma
Triamcinolone NASACORT*	Allergic rhinitis, Asthma

- Do NOT relax airway smooth muscle directly but **reduce bronchial reactivity** and reduce the frequency of asthma exacerbations if taken regularly

→ indirect effect

- They inhibit the release of arachidonic acid through inhibition of phospholipase A2, thereby producing **direct anti-inflammatory** properties in the airways

↳ B2-agonists بعكس



To be effective in controlling inflammation, these agents must be used regularly.

After several months of regular use, ICS reduce the hyperresponsiveness of the airway smooth muscle to a variety of

Agents used for Asthma:
Inhaled corticosteroids (ICS)

INHALED CORTICOSTEROIDS	
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- ICS are the **drugs of choice for long-term control in patients with persistent asthma**

مهمة

- **Potentiation** of the effects of β-receptor agonists

- Treatment of exacerbations or severe persistent asthma may require the addition of a short course of oral or intravenous corticosteroids.

ضروري نعرف انه Oral CS او IV CS ممنوع استخدمهم ب كورسات طويلة و فترات طويلة و السبب هو انه side effect تبعتهم خطيرة و ممكن تعمل disregulation في الهرمونات

Agents used for Asthma:
Inhaled corticosteroids (ICS)

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Triamcinolone NASACORT*	Allergic rhinitis, Asthma

Routes of administration

I. Inhalation → long term use, ↓ side effects.

This formula has markedly reduced the need for systemic corticosteroid (less side effects) but appropriate inhalation technique is critical to the success of therapy

II. Oral/systemic → Short term use, Severe ä

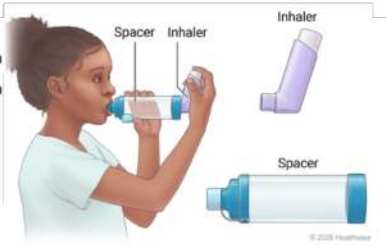
Patients with a severe exacerbation of asthma may require IV methylprednisolone or oral prednisone to reduce airway inflammation.

In most cases, suppression of the hypothalamic–pituitary–adrenal cortex axis does not occur during the oral prednisone "burst" (short course) typically prescribed for an asthma exacerbation. Thus, a dose taper is unnecessary prior to discontinuation.

الدكتور حكى: لو جبت سؤال، و العلاج حيكونو بشري، هل بنختار Oral أو inhaled؟
أكيد inhaled.

Agents used for Asthma:

Inhaled corticosteroids (ICS)



لهيك بستعمله للأطفال

Adverse effects

- ICS, particularly if used with a spacer, have few systemic effects.
- Deposition (ترسيب) on the oral and laryngeal mucosa can cause **oropharyngeal candidiasis** (due to local immune suppression) and **hoarseness**.
- Patients should be instructed (تعليمات) to rinse (غسل) the mouth in a "**swish-and-spit**" method with water following use of the inhaler to decrease the chance of these adverse events.
- Chronic maintenance with oral corticosteroids should be reserved for patients who are not controlled on an ICS.

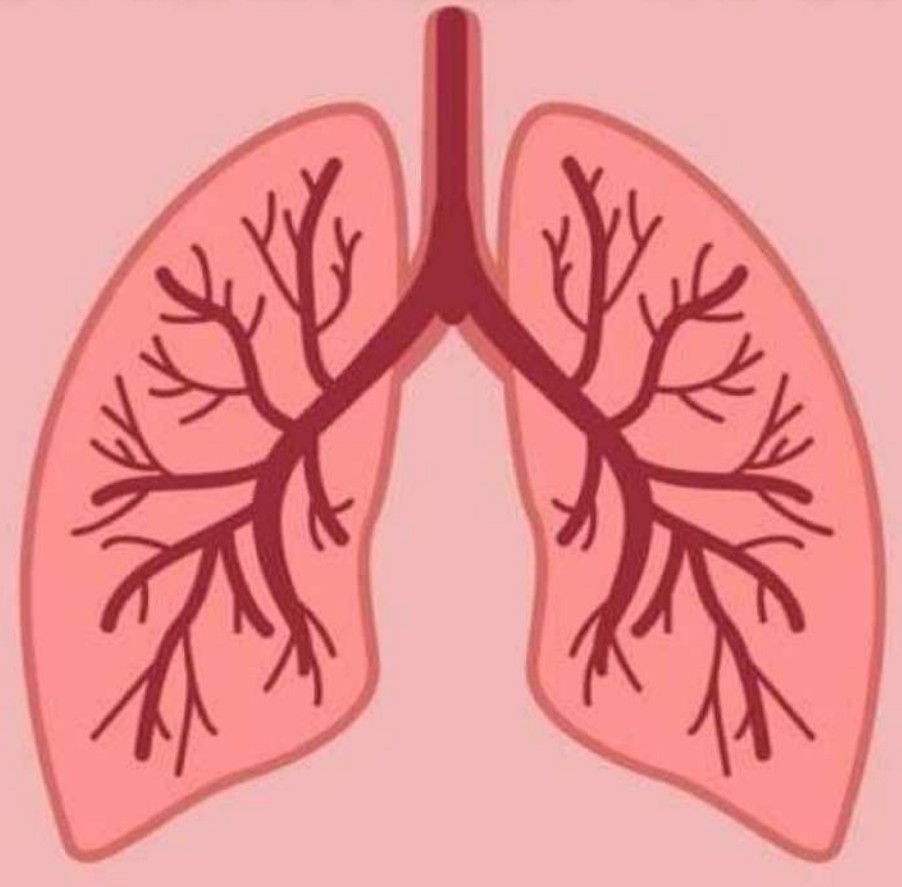
***Oral or parenteral corticosteroids have a variety of potentially serious adverse effects, whereas Inhaled CS, particularly if used with a spacer, have few systemic effects.**

← oropharyngeal candidiasis

Swish and spit method ←

النادي الطبي

RESPIRATORY SYSTEM



SUBJECT : Pharmacology

LECTURE : 3

DONE BY : Johainah Taha

Agents used for Asthma: Alternative drugs

- Useful for treatment of asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to corticosteroid treatment.
- Should be used in conjunction with ICS therapy for most patients.

A. **Leukotriene ((LT) modifiers** (Zileuton, Zafirlukast, montelukast
B. **Cromolyn**
C. **Cholinergic antagonists** (ipratropium and Tiotropium)
D. **Theophylline**
E. **Monoclonal antibodies** (Omalizumab, mepolizumab, benralizumab and reslizumab)

Watch these videos !♡

www.youtube.com › watch
Leukotriene modifiers - Respiratory Pharmacology - Part 8
This video describes the **Leukotriene modifiers** used in Bronchial asthma and COPD in a simple and easy manner to...
YouTube · Pharma Topics · Sep 14, 2021
https://youtu.be/3IDcYS_Ch8o

Leukotriene Modifiers: Nursing Pharmacology
Osmosis from Elsevier
7.8 ألف مشاهدة • قبل 9 أشهر
https://youtu.be/Srwm1yK45w0

www.youtube.com › watch
Cromolyn Mnemonic for Nursing Pharmacology (NCLEX)
Study this **Cromolyn** NCLEX **mnemonic** and other **mnemonics** with Pixorize.**Cromolyn** is a medication used to treat asthma. I...
YouTube · Pixorize · Jun 6, 2022
6 key moments in this video
https://youtu.be/aVxToQ4h0iI

Agents used for Asthma:

اقرأوا الشرح بالأول

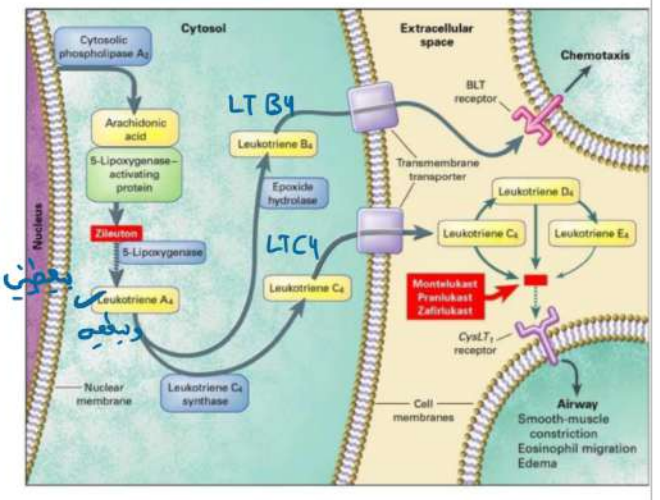
Leukotriene modifiers

➢ LTB4 and the cysteinyl leukotrienes (LTC4, LTD4, and LTE4) are **products of the 5-lipoxygenase pathway** of arachidonic acid metabolism and part of the inflammatory cascade.

➢ 5-Lipoxygenase is found in cells of **myeloid** origin, such as mast cells, basophils, eosinophils, and neutrophils.

➢ **LTB4** is a potent chemoattractant for **neutrophils** and **monocytes,** stimulates production of proinflammatory cytokines.

➢ **cysteinyl leukotrienes constrict** bronchiolar smooth muscle, **increase** endothelial permeability, **promote** mucus secretion, eosinophil recruitment and airway remodeling in chronic asthma



**Leukotrienes are chemicals your body releases when you come into contact with something you're allergic to. They can cause:

1-Coughing.
2-Extra mucus and fluid in your chest and throat.
3-Inflammation or swelling in your airway.
4-Tight muscles in your airway.
5-Tightness in your chest.
6-Wheezing or difficulty breathing.

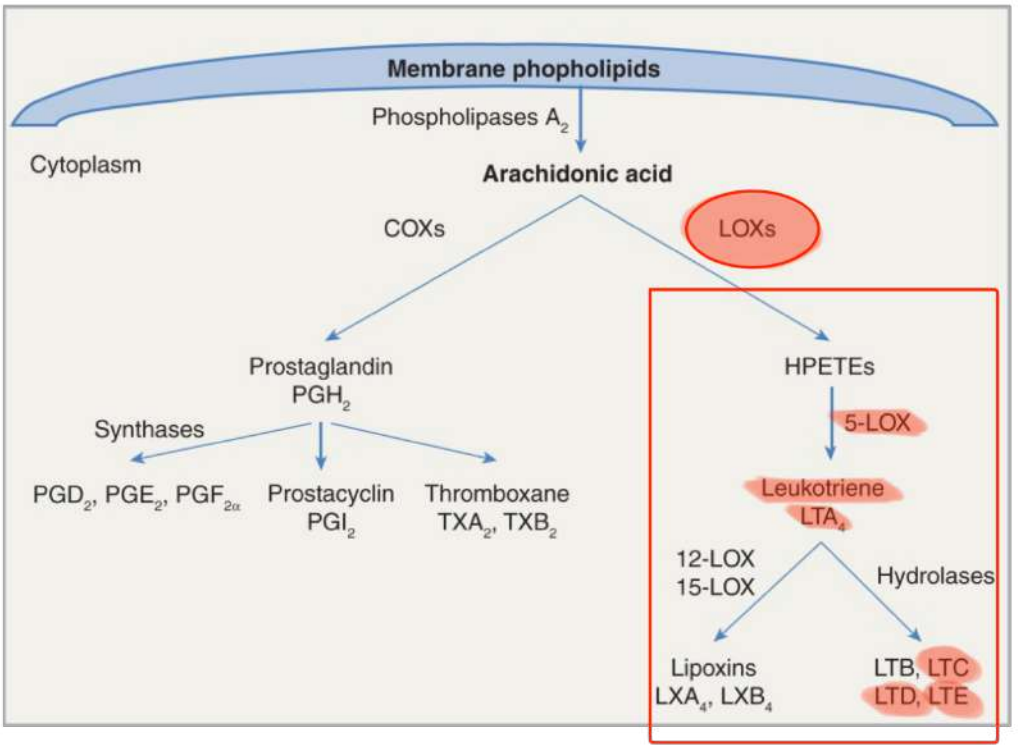
**Leukotriene modifiers, also called leukotriene receptor antagonists or leukotriene synthesis inhibitors, are medications that block the effect of leukotrienes or stop your body from producing them.

**Names of specific leukotriene modifiers include:

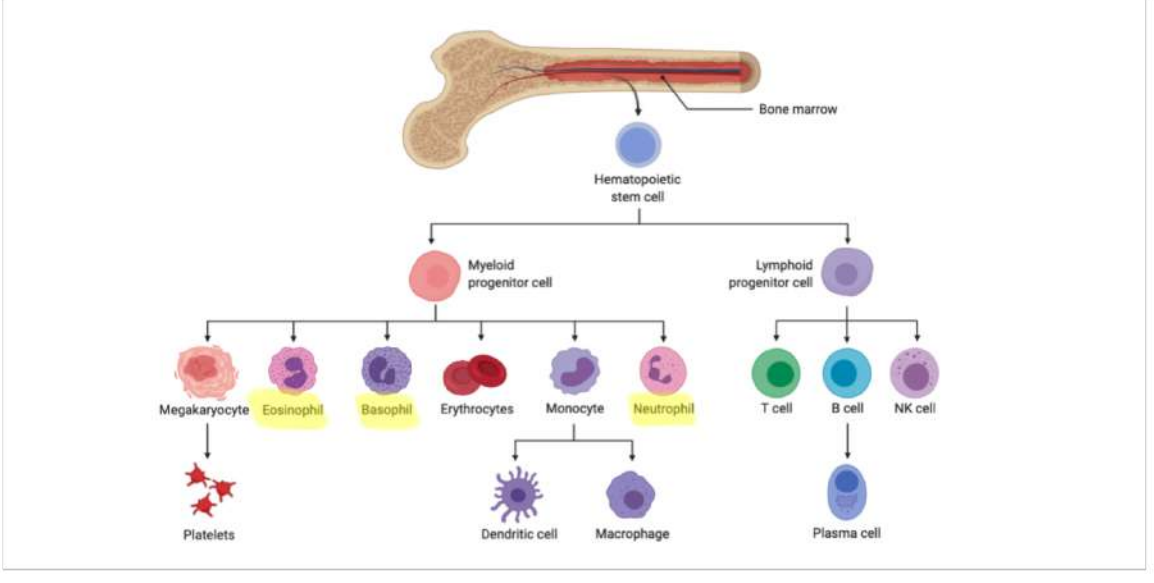
1-Montelukast
2-Zafirlukast
3-Zileuton

الان بدنا نفسر السلايدات و حأذكركم بشوية باثو

Leukotrienes (LT) 4 and the cysteinyl leukotrienes, LTC4 , LTD4 , and LTE4 , are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade.



5-Lipoxygenase is found in cells of myeloid origin, such as mast cells, basophils, eosinophils, and neutrophils.



إذا تأنيث الواء بكون عكس الجدول

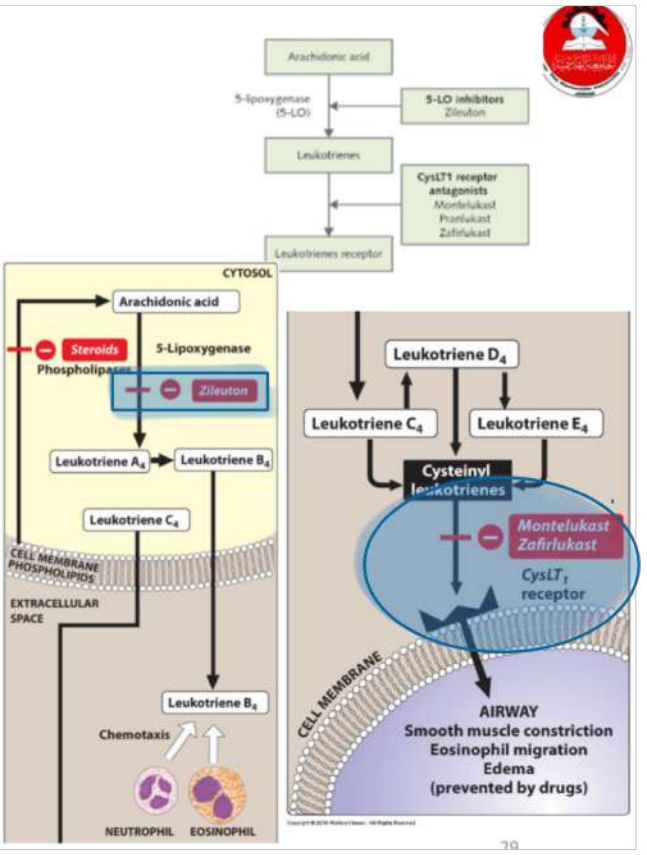
*LTB4 -> is a potent chemoattractant for neutrophils and eosinophils

*the cysteinyl leukotrienes -> constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucus secretion.

هسا ارجعوا للسلايد الي فوق

Agents used for Asthma:
Leukotriene modifiers

- ✓ Zileuton is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of **both** LTB4 and the cysteinyl leukotrienes.
- ✓ Zafirlukast and montelukast are selective antagonists of the cysteinyl leukotriene-1 receptor (CysLT1), and they block the effects of cysteinyl leukotrienes. (Approved for the prevention of asthma symptoms).
- ✓ Should not be used in situations where immediate bronchodilation is required.
  له مباشر
- ✓ Leukotriene receptor antagonists have also shown efficacy for the prevention of exercise-induced bronchospasm.



an Al Shboul ©

المهم نعرف الtarget لكل دواء و اسمه و متى بنستعمله

Agents used for Asthma:
Leukotriene modifiers

Pharmacokinetics

I can not use it in emergency

- These agents are orally active and highly protein bound.
- Food يضعف impairs the absorption of **zafirlukast**.
- Undergo extensive **hepatic** metabolism (zileuton and zafirlukast reported with liver toxicity).

لهيك اي شخص عنده مشكلة بال liver بدي اكون حذرك معه

- Montelukast is the most prescribed (taken without regard to meals+ once-daily treatment).

Most commonly used
Be carefull, if we want to inhibit LTB4, the most used drug is Zileuton

Zileuton and its metabolites are excreted in urine, whereas zafirlukast, montelukast, and their metabolites undergo biliary excretion

Agents used for Asthma:
Leukotriene modifiers

Adverse effects

- Elevations in serum hepatic enzymes>> requiring periodic monitoring and discontinuation when enzymes exceed three to five times the upper limit of normal.

خلي عينك عالliver function و انت بتعالج

- Headache and dyspepsia.

- Zafirlukast is an inhibitor of cytochrome P450 (CYP) isoenzymes 2C8, 2C9, and 3A4.

هاي الجزئية مهمة كثير كثير حيجي عليها سؤال حتى، لو الدكتور جاب سؤال انه في مريض بيوخد LT modifier و بيوخد معه دواء x الي بتكسر من واحد من الisoenzymes الي ذكرناهم فوق

شو حيكون تأثير الدواء x عالمريض ؟
اكيد تأثيره حيزيد بسبب انه ما في شي يكسر الدواء و هون انا بخاف من موضوع الtoxixity

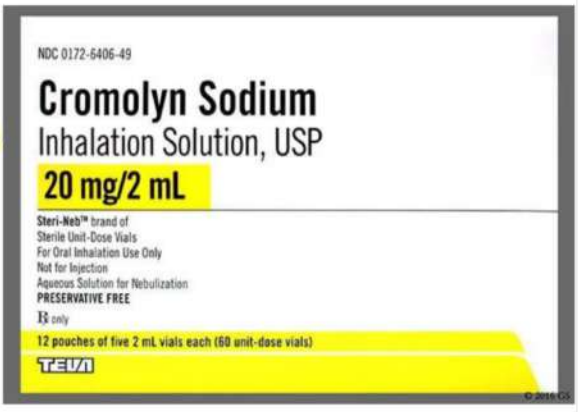
صياغة المعلومة موجودة تحت و عليها هايلايت و هي من الكتاب

*Zafirlukast is an inhibitor of cytochrome P450 (CYP) isoenzymes 2C8, 2C9, and 3A4, and zileuton inhibits CYP1A2.

*Coadministration with drugs that are substrates of these isoenzymes may result in increased effects and/or toxicity.

Agents used for Asthma:
Cromolyn

- ✓a prophylactic (وقائي) anti-inflammatory agent that ① inhibits mast cell degranulation and ② release of histamine.
- ✓An alternative (prophylaxis) therapy for mild persistent asthma and is available as a nebulized solution. (خفيفة + مستمرة)
- ✓NOT a bronchodilator>> NOT useful in managing an acute asthma attack.
- ✓Short duration of action>>dosing three or four times daily
- ✓Adverse effects are minor and include cough, irritation, diarrhea, and unpleasant taste.



Short duration of action = not used in emergency
Used in allergic asthma but no acute attack, and used in allergic rhinitis

Agents used for Asthma: muscarinic antagonist

SHORT-ACTING ANTICHOLINERGIC
Ipratropium ATROVENT
LONG-ACTING ANTICHOLINERGIC (LAMA)
Tiotropium SPIRIVA

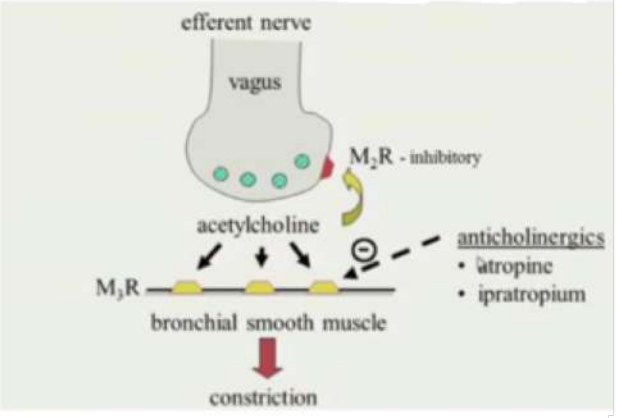
- Inhaled ipratropium is **NOT** recommended for the **routine** treatment of **acute** bronchospasm in asthma, why? its onset is much slower than that of inhaled SABAs
- useful in patients who are unable to tolerate a SABA or patients with asthma–COPD overlap syndrome.
- Tiotropium can be used as an add-on treatment in adult patients with severe asthma and a history of exacerbations.
- Adverse effects:

xerostomia and bitter taste are related to local anticholinergic effects.

جفاف الفم ← xerostomia

مر ← bitter taste

They are not the first line in asthma
But their combinations are the first line in COPD



Agents used for Asthma: muscarinic antagonist

- Atropine, causes bronchodilation at a lower dose than that needed to cause an increase in heart rate.

- Atropine selectivity effect can be **increased** further by administering the drug by inhalation or by use of ipratropium bromide.

- ipratropium bromide is poorly absorbed into the circulation and does not readily enter the central nervous system (even inhalation of high doses)

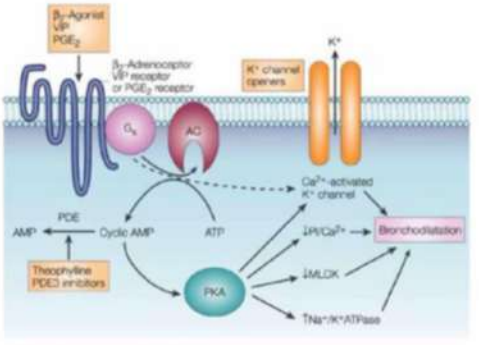
الدكتور ما ركز على هاي السلايد كونه
ال atropine لا يفصل استعماله
بس اقرأوها للاحتياط

Agents used for Asthma: Theophylline

- bronchodilator that relieves airflow obstruction in chronic asthma and decreases asthma symptoms.
- It may also possess anti-inflammatory activity, although the mechanism of action is unclear.

بالأصل موجود بالشاي

Theophylline



PDE=Phosphodiesterase
PKA=Protein Kinase A

It acts as a competitive nonselective phosphodiesterase inhibitor (inhibiting type III and type IV phosphodiesterase), which increases the concentration of intracellular cAMP, activates protein kinase A, inhibits TNF-alpha, and leukotriene synthesis, and also decreases inflammation and innate immunity.

- It was the mainstay of asthma therapy (replaced because of its narrow therapeutic window, adverse effect profile, and potential for drug interactions).

problem with the rate or rhythm of your heartbeat

- Overdose may cause seizures or potentially fatal arrhythmias.

هدول بهمهوا الدكتور

- Theophylline is metabolized in the liver and is a CYP1A2 and 3A4 substrate.

It is subject to numerous drug interactions. Serum concentration monitoring should be performed when theophylline is used chronically.

*mab = monoclonal antibody

Agents used for Asthma:
Monoclonal antibodies

- Omalizumab → IgE
- Mepolizumab
- Benralizumab
- Reslizumab) → IL5

- **Omalizumab** monoclonal antibody that selectively binds to human **immunoglobulin E (IgE)**>> **decreased** binding of IgE to its receptor on the surface of mast cells and basophils>>**limits the release of mediators** of the allergic response.
- Mepolizumab, benralizumab and reslizumab are monoclonal antibodies are of interleukin-5 **(IL-5) (antagonists).**
- IL-5 is the major cytokine involved in recruitment, activation, and survival of eosinophils in eosinophilic asthma.
- These agents are indicated for the treatment of **severe persistent asthma in patients who are poorly** controlled with conventional therapy.
- Their use is limited by the high cost, route of administration (IV for reslizumab and subcutaneous for others), and adverse effect profile.
- Adverse effects include serious anaphylactic reactions (rare), arthralgias, fever, rash, and increased risk of infections.
- New malignancies have been reported.

لأنهم بيرتبطوا بِ IL5 و IgE دون التمييز بين ما اذا كانت ناتجة بسبب asthma او اي شي تاني
لهيك لو تحولت الخلايا الى malignant ما حتلاقي شي يقاومها

سألت الدكتور عنها لهيك شكو الكومنات

نرجع نراجع هاي السلايد

All patients with asthma should have immediate access to an inhaled bronchodilator with a rapid onset of action for prompt relief of asthma symptoms, SABA: albuterol or levalbuterol)

Asthma management

- **Step 1:** SABA as needed (preferred) OR Low-dose ICS + Long- (fast) acting beta agonist (budesonide-formoterol or budesonide-albuterol) as needed
- **Step 2:** Low-dose ICS daily and separate SABA as reliever (preferred) OR Step 1 Low-dose ICS + long-(fast) acting beta agonist as needed OR leukotriene receptor antagonist (LTRA) daily with SABA as needed
- **Step 3:** Low-dose ICS-formoterol OR Low-dose ICS-LABA combination inhaler daily and separate SABA as reliever.
- **Step 4-6:** Medium-to high-dose ICS-LABA combination inhaler daily and separate SABA as reliever plus LAMA daily

CLASSIFICATION	BRONCHO-CONSTRICTIVE EPISODES	RESULTS OF PEAK FLOW OR SPIROMETRY	LONG-TERM CONTROL	QUICK RELIEF OF SYMPTOMS
Intermittent	Less than 2 days per week	Near normal*	No daily medication	Short-acting β_2 agonist
Mild persistent	More than 2 days per week, not daily	Near normal*	Low-dose ICS	Short-acting β_2 agonist
Moderate persistent	Daily	60%–80% of normal	Low-dose ICS + LABA OR Medium-dose ICS	Short-acting β_2 agonist ICS/*formoterol* is an alternative
Severe persistent	Continual	Less than 60% of normal	Medium-dose ICS + LABA OR High-dose ICS + LABA	Short-acting β_2 agonist ICS/*formoterol* is an alternative

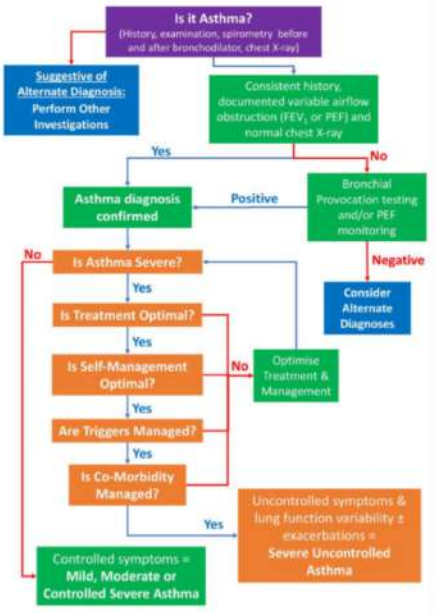
Diagnosis Of Asthma

- No precise (دقيق) test for the diagnosis

Clinically :

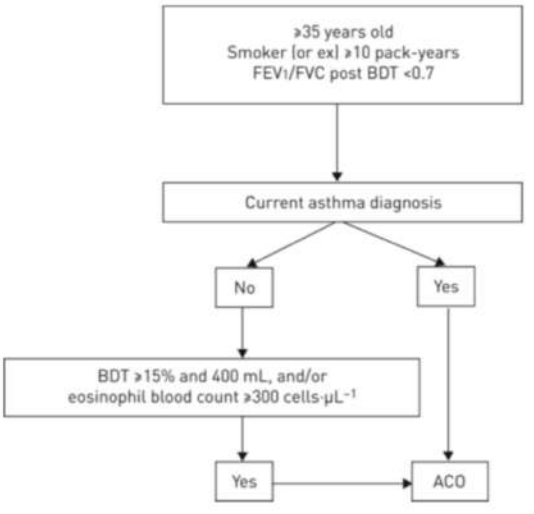
- Asthma may be suspected if there is a history of recurrent wheezing, coughing or difficulty breathing and these symptoms occur or worsen due to exercise, viral infections, allergens or air pollution

- Spirometry is used to confirm the diagnosis, and later in the management control.



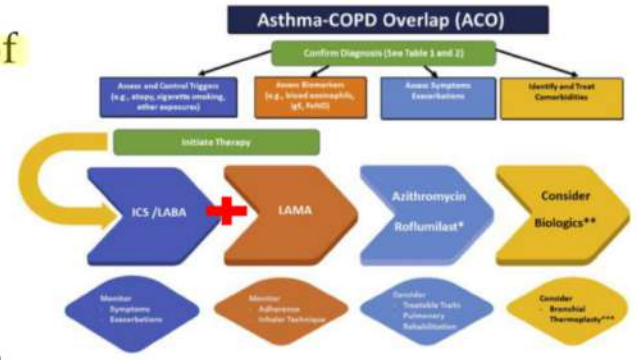
Asthma-COPD overlap syndrome (ACOS)

1. age >40 years
2. persistent airflow obstruction
3. history of asthma or evidence of partial bronchodilator reversibility
4. ≥10 pack-years tobacco smoking



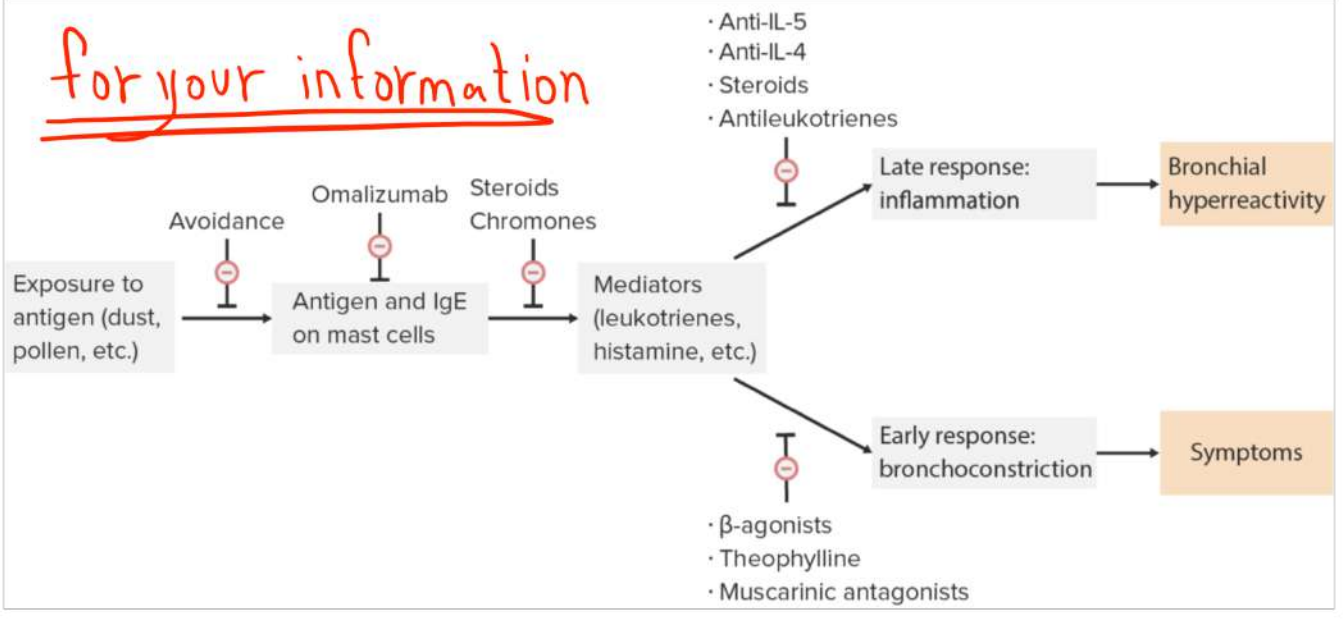
Asthma-COPD overlap syndrome (ACOS)

- Approach similar asthma: ICS
- Inhaled bronchodilator with rapid onset of action (SABA, SAMA combination) for as-needed symptom relief.
- Regular therapy ICS (low to moderate doses) (+ LABA and/or LAMA may be necessary to control symptoms.
- **LABA monotherapy should be avoided, as in asthma.**



Salmeterol Multicenter Asthma Research Trial (SMART) randomized trial comparing salmeterol (MDI) VS placebo. An interim analysis in 26,355 patients found an increase in **respiratory-related deaths and asthma-related deaths**

for your information



المطلوب اسم الدواء و الpathway الي بستهدفها

Agents under investigation

- Astegolimab: human IgG2 mAb (monoclonal anti-body), selectively inhibits the IL-33 receptor, ST2. (← pathway)

https://pubmed.ncbi.nlm.nih.gov/33872652/.

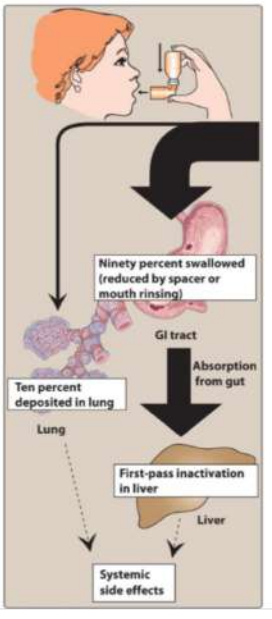
- Tozorakimab: mAb with a dual pharmacological profile that can inhibit IL-33 activities through the ST2 and RAGE/EGFR signalling pathways. To reduce excess inflammation and epithelial remodelling in IL-33-driven disease.
- https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A2397

Inhaler Techniques: Metered-dose inhalers (MDIs) & dry powder inhalers (DPIs)

Exhale before using the inhaler, and then begin to inhale slowly as they press the canister and continue inhaling slowly and deeply throughout actuation.

A large fraction (typically 80% to 90%) of inhaled medication (for example, corticosteroids) is either deposited in the mouth and pharynx or swallowed. The remaining 10% to 20% of a dose of inhaled glucocorticoids that is not swallowed reaches the site of action in the airway.

DPIs require a different inhaler technique. Patients should be instructed to inhale quickly and deeply to optimize drug delivery to the lungs. Patients using any type of inhaled corticosteroid device should be instructed to rinse the mouth after use to prevent the development of oral candidiasis.



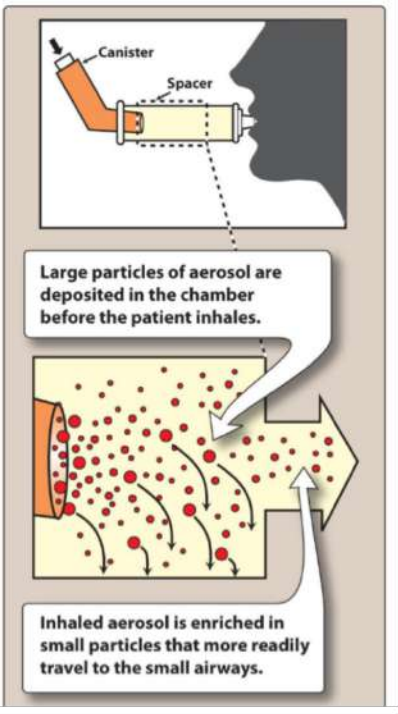
الدكتور حكى ما حيسأل عن التفاصيل لهيك افهموا الفكرة بشكل عام بس
ركز على الي عليه هايلايت

Inhaler Techniques: Spacers

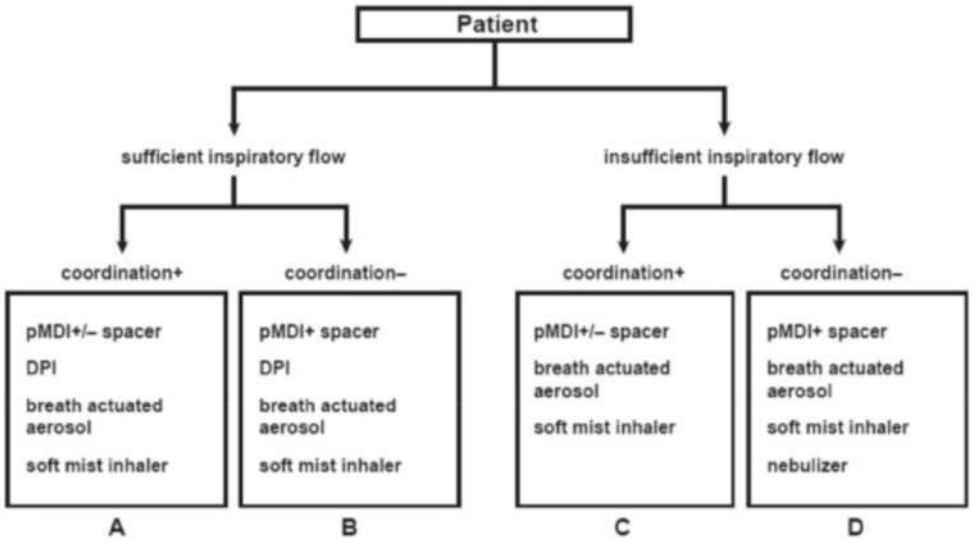
شرحنا عنه و حكينا انه بخفف من الeffect تبع الcorticosteroids

A spacer is a large-volume chamber attached to an MDI. The chamber reduces the velocity of the aerosol before entering the mouth, allowing large drug particles to be deposited in the device. The smaller, higher-velocity drug particles are less likely to be deposited in the mouth and more likely to reach the target airway tissue.

Patients should be advised to wash and/or rinse spacers to reduce the risk of bacterial or fungal growth that may induce an asthma attack.



Inhaler Techniques: Metered-dose inhalers (MDIs) & dry powder inhalers (DPIs)



- https://www.stlouischildrens.org/health-resources/pulse/medical-animation-inhalers
- https://www.youtube.com/watch?v=jSkwBoed6Tw

Quiz Time ⏳

1)A 31-year-old man is brought to the emergency department complaining of dyspnea. He has a history of asthma and has had multiple asthma attacks requiring intubation for airway maintenance. He is noncompliant with his medications prescribed for this condition.Physical examination reveals a young man in acute distress. His room air oxygen saturation is 87%. In addition to administration of oxygen, immediate drug administration of albuterol should be administered by which of the following routes?
(A) Inhalation
(B) Intranasal puff metered dose
(C) Subcutaneous
(D) Sublingual
(E) Topical
Answer = A

2)A 7-year-old boy is brought to the emergency department by his parents after being stung by a bee. The parents say he is allergic to bee stings, and the patient is having great difficulty breathing. Epinephrine is administered immediately. His symptoms improve as molecules of epinephrine bind to beta 2-receptors in bronchiolar smooth muscle. Which of the following drugs also stimulates these receptors?
(A) Acebutolol
(B) Phenylephrine
(C) Prazosin
(D) Salmeterol
(E) Timolol
Answer = D

3)A 23-year-old male college graduate student with a history of asthma presents to the ambulatory care clinic for follow-up. He uses a beta 2-agonist via inhaler when he has an attack. The treating physician should be alert to which of the following possible findings on examination and laboratory studies?
(A) Bradycardia
(B) Hyperglycemia
(C) Hyperkalemia
(D) Hypermagnesemia
(E) Hypertension
Answer = B

4)A 47-year-old man presents to the ambulatory care center with symptoms of hypoglycemia and is found to have an insulinoma. His medical history is significant for occasional asthma to which he treats using an albuterol inhaler, and an MI for which he takes daily low-dose aspirin. Because he takes aspirin, he is not able to immediately undergo surgery. The physician prescribes diazoxide for therapy until the tumor can be removed. Diazoxide stimulates potassium channels leading to inhibition of insulin release. Which of the following is most likely to occur in this patient as a result of diazoxide therapy?
(A) Bronchoconstriction
(B) Hypertension
(C) Hypoglycemia
(D) Hypotension
(E) Seizures
D

5)A 42-year-old woman with a history of asthma has an attack and is brought to the emergency department for evaluation and treatment. She is wheezing and is short of breath. What is the most likely pathophysiology of this condition?
(A) Bronchodilation
(B) Increased secretion of mucus
(C) Inflammation of the bronchial serosa
(D) Relaxation of bronchial smooth muscle
Answer = B

6)A 5-year-old boy is brought to the clinic by his parents who say that he often has trouble catching his breath when he has been playing hard outside. He is allergic to peanuts. At the moment, he is breathing fine. Which of the following drugs would dilate his bronchioles in an acute asthma attack?
(A) Albuterol
(B) Methacholine
(C) Neostigmine
(D) Nicotine
(E) Pilocarpine
Answer = A

7)Five patients undergo surgery for various reasons. Each patient has a particular prior medical history. Which of the following patients would be most problematic to the anesthesiologist if thiopental is used during the surgery?
(A) A 5-year-old boy with recurrent otitis media
(B) A 7-year-old boy with recurrent sinusitis
(C) A 9-year-old boy with asthma
(D) A 12-year-old boy with anemia of chronic disease
(E) A 15-year-old boy who has never received anesthesia
Answer = C

8)A 4-year-old boy is hospitalized on the pediatric service with cough, runny nose, and chest pressure. Concern for respiratory syncytial virus is brought up by the treating physician. Treatment with zanamivir is undertaken. Which of the following underlying conditions can worsen bronchospasm in this patient?
(A) Adenoiditis
(B) Asthma
(C) Floppy tongue syndrome
(D) Pharyngitis
(E) Tracheitis
Answer = B

9) 6-year-old boy presents to his pediatrician for follow-up of recurrent hay fever and asthma. He usually has two to three attacks per week. For symptom control, he uses an albuterol inhaler, but his parents would like to try something more. They would like him to take something that would lessen the amount of attacks he has. Although corticosteroids would probably work best for prophylaxis, they are contraindicated in children. Which of the following drugs would decrease the amount of asthma attacks by preventing an arachidonic acid derivative from binding to its receptor?
(A) Aspirin
(B) Celecoxib
(C) Ipratropium
(D) Montelukast
(E) Zileuton
Answer = D

10) A 27-year-old man with recurrent asthma attacks is being considered for preventative therapy with cromolyn sodium. This agent is not effective as an acute treatment of an asthma attack because of the lack of which of the following properties?
(A) Anti-inflammatory
(B) Bronchodilator
(C) Immune modulator
(D) Mast cell stabilizer
(E) Neutrophil inhibitor
Answer = B

11) A 48-year-old man with a known history of asthma takes daily theophylline. He is found unconscious in his bathroom with an open bottle of theophylline that is now empty nearby. He is found by EMS to be apneic and pulseless. What is the most likely cause of death in this patient?
(A) Apnea
(B) Cardiac arrhythmia
(C) Pulmonary embolism
(D) Seizures
(E) Tetany
Answer = B

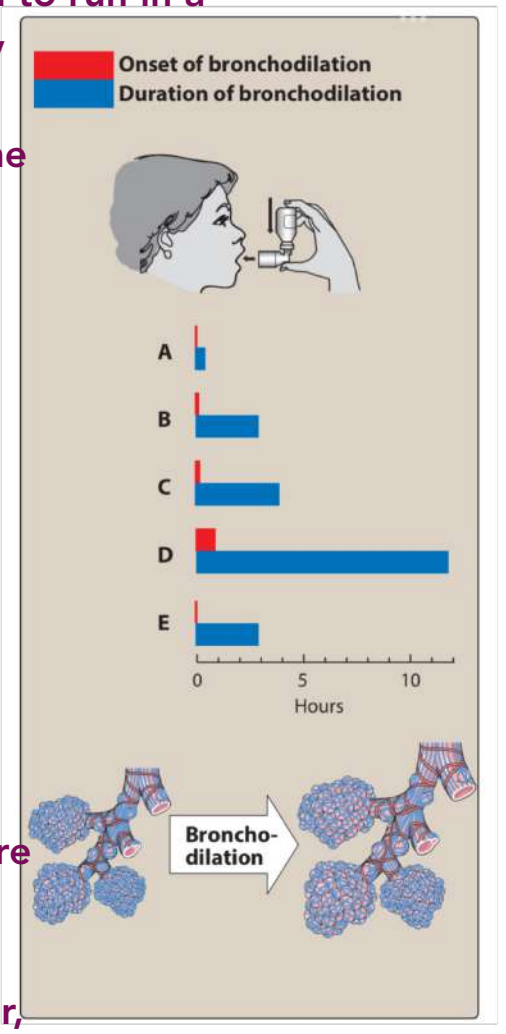
12) A 52-year-old man with asthma treated with a beta 2-agonist via inhaler has been having difficulty with therapy because of persistent changes in blood pressure, nausea, vomiting, and hypomagnesemia. Which of the following medications would be best for this patient?
(A) beta 2-Agonist via inhaler every other day
(B) beta 2-Agonist via inhaler every third day
(C) beta 2-Agonist via inhaler twice daily
(D) Change to ipratropium
(E) Change to epinephrine
Answer = D

13) A 13-year-old male has begun having spells of wheezing and difficulty breathing while playing outside. He is diagnosed with asthma and given an inhaler to treat acute attacks. His medication is working well, but he would also like something to prevent attacks from happening. Which of the following drugs would be best to add to his regimen?
(A) Albuterol
(B) Epinephrine
(C) Ipratropium
(D) Isoproterenol
(E) Salmeterol
Answer = E

14) A 13-year-old boy with moderate asthma presents to the clinic for follow-up. His symptoms appear to be better controlled since adding salmeterol to his regimen. He has had to use his rescue inhaler once over the past 2 weeks during exertion. His breathing at night has improved as well. How does salmeterol exhibit its beneficial effects for asthma?
(A) Long-acting beta1-agonist
(B) Long-acting beta1-antagonist
(C) Long-acting beta1- and %2-agonist
(D) Long-acting beta2-agonist
(E) Long-acting beta 2-antagonist
Answer = D

15) A 24-year-old man presents to the primary care clinic for follow-up of his asthma. He has had asthma since he was 8 years old and requires daily treatment for his symptoms. He often has nighttime awakenings with coughing spells. On physical exam, diffuse wheezing is heard bilaterally. He is willing to try anything to improve his symptoms. The physician decides to add cromolyn to his regimen. What is the mechanism of action of cromolyn?
(A) Blocks leukotriene receptors
(B) Inhibits endothelin-1 receptors
(C) Mast cell stabilizer
(D) Muscarinic antagonist
(E) Phosphodiesterase inhibitor
Answer = C

16) A 34-year-old man with exercised-induced asthma is searching for a bronchodilator that will allow him to run in a marathon. The event will take him approximately 6 h and 30 min to complete. The following diagram shows five bronchodilators. Which of the following agents will provide him with the most efficacious therapy during his run?



(A) Letter A
(B) Letter B
(C) Letter C
(D) Letter D
(E) Letter E
Answer = D

17) A 6-year-old boy is brought to his primary care physician with a history of hay fever and asthma. He usually has two to three attacks per week. For symptom control, he uses an albuterol inhaler, but his parents would like to try something more. They would like him to take something that would lessen the amount of attacks he has. Although corticosteroids would probably work best for prophylaxis, they are contraindicated in children. He is instead give montelukast.

How does montelukast works?
(A) Blocks leukotriene receptors
(B) Blocks muscarinic acetylcholine receptors
(C) Inhibits COX-1 and COX-2
(D) Inhibits COX-2 only
(E) Inhibits lipoxygenase
Answer = A

انتهى التفريغ الحمدلله 🫶🏻

ما تنسوني بدعوة بهاي الأيام الفضيلة 🙏🏻

بالتوفيق ❤️❤️

#النادي_الطبي❤️