**Done by:Noor Marzooq & Zeina Yassin**

# *Pharmacological Management of Bronchial Asthma*

*Bronchial asthma is a condition characterized by high responsiveness of the airway to a variety of stimuli, the result of which is widespread narrowing of the airways, **that changes in severity**either spontaneously or as a result of treatment (i.e: reversible).

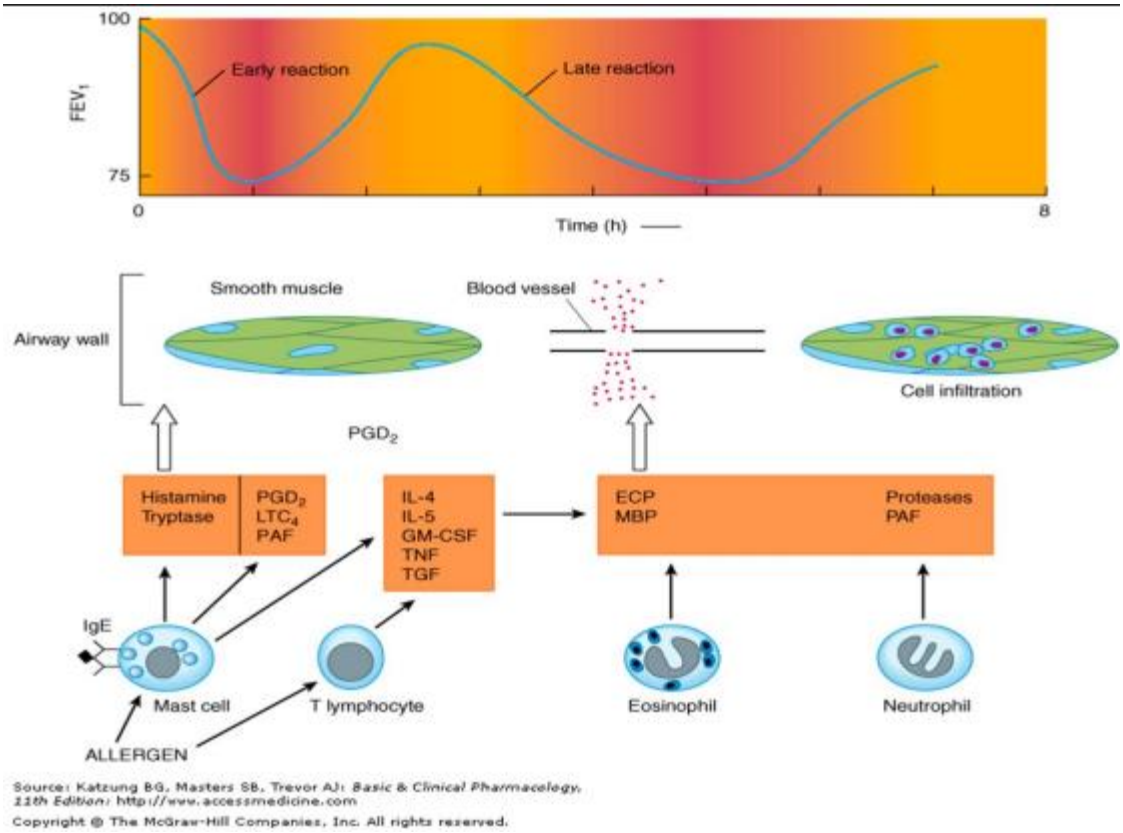
* **Pathology**:
1. Bronchospasm leading to narrowing of the airways.
2. Mucosal edema leading to mucosal thickening and narrowing of airways
3. Mucous secretion leading to mechanical occlusion.
4. Deposition of collagen beneath the endothelium.
5. Hyperplasia of vessels, smooth muscle, secretory glands and goblet cells.

*** Characterized by:**
1. Attacks of coughing 2. Shortness of breath – difficulty in breathing 3. Chest tightness
4. Wheezing

***Bronchoconstrictors:**
Acetylcholine, β-blockers, Adenosine, α-adrenergic agonists, Prostaglandins F2α & D2 , Serotonin, Bradykinin, Histamine, Leukotrienes C4 & D4 , Platelet-activating factor, …

***Inflammation**:
Results from IgE-mediated allergy, or viral infection

****Immunologic Model:**
• Bronchial Asthma is mediated by IgE antibodies bound to airway mast cells.
• On re-exposure to an antigen, Ag-Ab interaction takes place on the surface of mast cells leading to release of mediators: histamine, leukotrienes C4 & D4 , PGD2 , eosinophil chemotactic factor, neutrophil chemotactic factor and many others.
• These agents produce contraction of airway smooth muscle, mucosal edema, cellular infiltration and increased mucus secretion. 6 Pathogenesis of Bronchial Asthma
• Bronchoconstriction appearing within 10-20 min of exposure to a provoking factor and mediated by the release of bronchoconstrictors from mast cells is called the “early asthmatic response”.
• In some patients a “late asthmatic response” may occur 3-6 hours after exposure and is due to airway inflammation, cellular infiltration of airway mucosa, mucous hypersecretion and sustained bronchoconstriction. 7 Pathogenesis of Bronchial Asthma
• Eosinophiles are involved in this response through generation of eosinophil major basic protein and eosinophil cationic protein which produce epithelial sloughing and increase in the contractile responsiveness of the airway smooth muscle.
• Cytokines produced by TH2 lymphocytes, GM-CSF, TNF, TGF, Interleukins 4, 5, 9, 13 attract and activate eosinophiles and neutrophiles, stimulate IgE production by B lymphocytes, and stimulate mucus production by bronchial epithelial cells.




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



**Pathogenesis of Bronchial Asthma :**

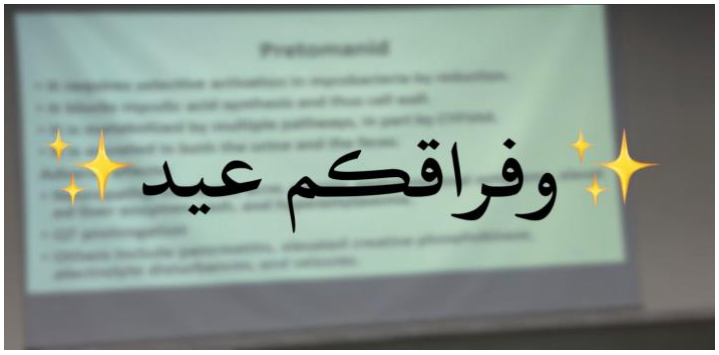
• A major limitation to this classic conception of asthma as an allergic disease is that it applies only to **a subgroup of patients with evidence of allergy**.

• The allergen challenge **model fails to** account for all the features of the condition even in allergic asthmatics.

• Allergic asthma accounts **for a great proportion of asthma t**hat develops in childhood, but a smaller proportion of adult-onset asthma. 10 Pathogenesis of Bronchial Asthma

• Thus, modifying terms to describe asthma in different patients include: "extrinsic" vs "intrinsic," "aspirin-sensitive," "adultonset," "post-viral," and "obesity-related."

• Many pathways and mechanisms other than production of IgE and activation of mast cell degranulation are involved in asthma's pathogenesis, and most asthma attacks are not triggered by inhalation of allergens, but instead by viral respiratory infections.



## Sympathomimetics (Beta2-Adrenergic Receptor Selective Drugs)

| Feature | Details |
|---|---|
| **Types (Drug Names)** | **-Fast-acting (FABs):** Albuterol and Terbutaline(maximal within 15 minutes and persists for 3 - 4 hours.)<br>**-Long-acting (LABAs):** Salmeterol and Formoterol(durations of action ~ 12 hour . They have high lipid solubility)<br>**-Ultralong-acting:** Indacaterol, Vilanterol, and others(once a day, masks symptoms of bronchial inflammation, used only with an inhalational corticosteroids , may be used as monotherapy for (COPD)). |
| **Mechanism of Action** | These drugs increase cAMP levels in bronchial smooth muscle by stimulating adenylyl cyclase. They cause relaxation of airway smooth muscle (bronchodilation), inhibit the release of bronchoconstrictor substances from mast cells, may inhibit microvascular leak, and may increase mucociliary transport by increasing ciliary activity. |
| **Therapeutic Uses** | -They are the most widely used agents for the treatment of **acute** bronchoconstriction.<br>-given by inhalation or nebulization<br>-Because they have no anti inflammatory action, they should not be used as monotherapy for asthma, and should be combined with corticosteroids.<br>Additional uses include chronic obstructive pulmonary disease (COPD) and inhibiting uterine contractions associated with premature labor. |
| **Adverse Effects** | Lactic acidosis (reflecting direct effects on cellular metabolism), hypokalemia (driving potassium into cells via Na^+/K^+-ATPase pump in skeletal muscle), skeletal muscle tremor, occasional weakness, and tachyphylaxis (reduction in response after several days of regular use). |

## Methylxanthines(Theophylline)

| Feature | Details |
|---|---|
| **Types (Drug Names)** | Theophylline, Caffeine, and Theobromine. |
| **Old Uses** | They were a mainstay of treatment, though their use has declined with the demonstration of greater efficacy in inhaled \beta_2-agonists and glucocorticoids. |
| **Therapeutic Uses (theophylline)** | Occasionally used for patients with bronchial asthma and to treat apnea in premature infants. |
| **Adverse Effects** | Nausea, vomiting, tremulousness, convulsions, arrhythmias, and drug-drug interactions. They have a narrow therapeutic index requiring monitoring of serum concentrations. |

## Antimuscarinic Agents

| Feature | Details |
|---|---|
| **Types (Drug Names)** | **-Short acting (4 hours):** Ipratropium bromide.<br>**-Long acting (24 hours or more):** Tiotropium bromide. |
| **Mechanism of Action** | These are quaternary ammonium compounds that block M_3 muscarinic receptors. This blocks airway smooth muscle contraction and the increase of mucus secretion produced by acetylcholine.<br>- administered by inhalation, and not suitable for oral administration<br>- Do not cross the blood brain barrier<br>-Do not inhibit mucociliary clearance, in contrast to atropine |
| **Therapeutic Uses** | Mainly used for treatment of COPD with a reversible obstruction component. They can also be used in bronchial asthma, often combined with other drugs. |
| **Adverse Effects** | Dry mouth (managed with a spacer or dose reduction) and a potential associated risk of dementia with advancing age**. |
| **NOTES** | -The magnitude of action is proportional to the contribution of parasympathetic stimulation to airway smooth muscle tone in asthmatic patients. |

## Corticosteroids

| Feature | Details |
|---|---|
| **Types (Drug Names)** | **Inhaled:** Beclomethasone dipropionate, Triamcinolone acetonide, Budesonide, Flunisolide, Fluticasone.<br>**Systemic:** Prednisone (PO), Methylprednisolone (IV). |
| **Mechanism of Action** | - Action starts after several hours<br>They inhibit the infiltration of asthmatic airways by lymphocytes, eosinophils, and mast cells. They inhibit production of pro-inflammatory cytokines, inhibit phospholipase A2 (blocking arachidonic acid metabolites like PGs and LTs), and may inhibit IgE synthesis. |
| **Therapeutic Uses** | First-line therapy for bronchial asthma when used in combination with \beta_2-agonists. Do not relax airway smooth muscle but They reduce bronchial hyper-reactivity, reduce exacerbations, and improve indices like severity of symptoms and quality of life.<br>- Do not relief the acute episode<br>- contraction of engorged vessels in the bronchial mucosa. |
| **Adverse Effects** | Oropharyngeal candidiasis, dysphonia (hoarseness of voice due to local effect on vocal cords), and suppression of the hypothalamic-pituitary-adrenal axis. |

## Mast Cell Stabilizers

| Feature | Details |
|---|---|
| **Types (Drug Names)** | Cromolyn Na and Nedocromil Na. |
| **Mechanism of Action** | These drugs act by inhibiting mast cell degranulation. They have no direct bronchodilator action but inhibit both antigen and exercise-induced bronchospasm. |
| **Therapeutic Uses** | Once widely used for asthma management (especially in children). Available as solutions for nebulization, nasal sprays for allergic rhinoconjunctivitis, oral solution. and ophthalmic solutions. |

## Leukotriene Pathway Inhibitors

| Feature | Details |
|---|---|
| **Types (Drug Names)** | **5-Lipoxygenase inhibitors:** Zileuton.<br>**-LTD_4 receptor antagonists:** Zafirlukast and Montelukast.<br>**NOT first-line agents for bronchial asthma. |
| **Mechanism of Action** | -**Zileuton** blocks the production of LTC4, LTD4, LTE4, LTB4.<br>-**Zafirlukast** and **Montelukast** block the LTD4 receptor to interrupt bronchoconstriction, mucosal edema, and mucus hypersecretion. |
| **Therapeutic Uses** | -Both improve asthma control , reduce frequency of exacerbations ,blocking airway response to exercise, aspirin and antigen challenge<br>-Effective when taken regularly **in outpatients**<br>-Overall effect is **less** than that of inhaled corticosteroids, but **equally** effective in reducing frequency of exacerbations<br>-Advantage: **PO** administration |
| **ROLE IN: Aspirin-exacerbated respiratory disease (AERD)** | -Asthma, chronic rhinosinusitis with nasal polyposis<br>-result from inhibition of cyclooxygenase, shifting arachidonic acid metabolism from the prostaglandin to the leukotriene pathway.<br>-profound bronchoconstriction, nasal congestion.<br>-occurs in approximately 5- 10% of patients with asthma. |
| **Adverse Effects** | **Zileuton:** Liver toxicity and dyspepsia.<br>**Receptor blockers:** High risk of serious neuropsychiatric events (suicidality, nightmares, irritability, aggressiveness,sleep disturbance), behavioral problems in children, and fatal hepatic failure. |
| **NOTE** | -Leukotrienes are synthesized by (eosinophiles, mast cells, macrophages,basophiles)<br>-Leukotriene B4 (**LTB4** ) is a potent neutrophile chemoattractant<br>-**LTC4** , and **LTD4** exert bronchoconstriction, increased bronchial reactivity, mucosal edema, and mucus hypersecretion. |
| **Drug Interactions** | **Zileuton**: inhibition of the metabolism of theophylline, warfarin, propranolol, & terfenadine (inhibition of drug metabolizing isoenzymes (CYP3A4)).<br>**Receptor blockers**: increased plasma concentration of warfarin due to inhibition of the cytochrome P450 2C9 by zafirlukast.<br>**Erythromycin reduces their bioavailability. |

## Targeted Monoclonal Antibody Therapy

These agents target specific inflammatory pathways and are reserved for severe or poorly controlled asthma.

| Antibody Name | Target | Use |
|---|---|---|
| **Omalizumab** | **IgE**<br>-The portion of IgE that binds to its receptors (FcεR1 and FcεR2 receptors) on dendritic, basophiles, mast cells, other inflammatory cells. | - prevent mast cell degranulation.<br>-Used for moderate-to-severe allergic asthma & evidence of perennial allergic sensitization.<br>-Reduces the magnitude of both early and late bronchospastic responses to antigen challenge.<br>- Patients most likely to respond:<br>a.with a history of repeated and severe exacerbations<br>b.high corticosteroid requirement<br>c.poor pulmonary function.<br>- effective in chronic recurrent **urticaria, nasal polyposis and peanut allergy**<br>- lowers free plasma IgE to undetectable levels.<br>-Reduction in the frequency and severity of asthma exacerbation, and of corticosteroid requirements |
| **Mepolizumab / Reslizumab** | **IL-5**<br>- T2 helper cells secrete IL-5 as a proeosinophilic cytokine that results in eosinophilic airway inflammation | -some patients with severe asthma have airway and peripheral eosinophilia, driven by upregulation of IL-5.<br>-Improving pulmonary function and measures of asthma control, while preventing exacerbations in asthmatic patients with peripheral eosinophilia, as add-on therapy.<br>-Mepolizumab may be used for treatment of eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome (HES), and rhinosinusitis with nasal polyps.(DR. said that this note isn't IMP but take alook)<br><br>-These drugs may have a risk of anaphylaxis, or hypersensitivity.<br><br>-Reactivation of herpes zoster has been reported in some patients who received mepolizumab. |
| **Benralizumab** | **IL-5 Receptor** | |

| Antibody Name | Target | Use |
|---|---|---|
| **Dupilumab** | **IL-4/IL-13 Receptor (gainst the IL-4α co-receptor for both)** | -Reduce exacerbation frequency and improve pulmonary function and measures of asthma control.<br>-Used in patients with moderate-to-severe asthma, with an eosinophilic phenotype or corticosteroid-dependance.<br>-Indicated for moderate to severe atopic dermatitis, prurigo nodularis, rhinosinusitis with nasal polyposis, and eosinophilic esophagitis<br>-May cause a peripheral eosinophilia which is typically transient but in rare cases may persist<br>-Avoid initiation if baseline eosinophils are very elevated (>1500 eosinophils/μL). |
| **Tezepelumab-ekko** | **TSLP(Thymic Stromal Lymphopoietin)** which is an epithelial cytokine | -Treatment of severe asthma<br>-Blocking the target decreases several downstream inflammationassociated cytokines (IgE, IL-5, and IL-13) and biomarkers (peripheral and airway submucosal eosinophils and fractional exhalation of nitric oxide). |

**Monoclonal antibodies for use in asthma.**

| Antibody Name | Isotype | Target | Route of administration | Patient's age |
|---|---|---|---|---|
| Omalizumab | Humanized IgG1 | IgE | SC every 2-4 weeks | 6 years and older |
| Mepolizumab | Humanized IgG1 | IL-5 | SC every 4 weeks | 6 years and older |
| Benralizumab | Humanized IgG1 | IL-5 receptor | SC every 4 weeks for the first 3 doses, the every 8 weeks | 6 years and older |
| Rezlizumab | Humanized IgG4 | IL-5 | IV infusion every 4 weeks | 18 years and older |
| Dupilomab | Human IgG4 | IL-4 receptor | SC every other week | 6 years and older |
| Tezepelumab-ekko | Human IgG2 | TSLP* | SC every 4 weeks | 12 years and older |

*TSLP thymic stromal lymphopoietin

These are antiinflammatory therapy targeting specific inflammatory pathways.

**The doctor said that it is not important and advised us to focus on the information mentioned below; however, as a precaution, review it briefly.**

***** They can be administered either subcutaneously or intravenously, although subcutaneous administration is preferred. It is not a daily medication, but is given at intervals of weeks rather than days. This therapy is usually used for younger patients, including children from an early age.**

اللهم اجعل أجر هذا العمل صدقة جارية عن روح **عمر عطيه عوده المرابي**

اللَّهُمَّ اغْفِرْ له وَارْحَمْهُ، وَاعْفُ عنْه وَعَافِهِ، وَأَكْرِمْ نُزُلَهُ، وَوَسِّعْ مُدْخَلَهُ، وَ اغْسِلْهُ بمَاءٍ وَثَلْجٍ وَبَرَدٍ، وَنَقِهِ مِنَ الخَطَايَا كما يُنَقّى الثَّوْبُ الأبْيَضُ مِنَ الدَّنَسِ.

اللَّهُمَّ أبدله داراً خيراً من داره، وأهلاً خيراً من أهله، وأدخله الجنّة، وأعذه من عذاب القبر ومن عذاب النّار.

اللهمّ يمّن كتابه، ويسّر حسابه، وثقل بالحسنات ميزانه، وثبّت على الصراط أقدامه، وأسكنه في أعلى الجنات، بجوار حبيبك محمد صلّى الله عليه وسلم.

اللهم اغفر لحينا وميتنا وشاهدنا وغائبنا وصغيرنا وكبيرنا وذكرِنا وأنثانا اللهم من أحييته منا فأحيِه على الإسلام ومن توفيته منا فتوفه على الإيمان اللهم لا تحرمنا أجره ولا تضلنا بعده.

اللهم اغفر له وارفع درجته في المهديين، واخلفه في عقبه في الغابرين، واغفر لنا وله يا رب العالمين، وافسح له في قبره، ونوّر له فيه.

اللَّهُمَّ أنزل على أهله الصّبر والسلوان وارضهم بقضائك.

**اللهم لا تفجعنا بأنفسنا ولا أهلنا ولا أحبتنا، اللهم أعوذ بك من فواجع الأقدار ومن مصائب الدنيا وتقلب حوادثها، اللهم إنا نخاف الفقد فلا تحملنا ما لا طاقة لنا به.**