DRUGS FOR ASTHMA SUMMARY

الملخص شامل الأدوية فقط

Drugs for Asthma

Overview of the changing therapy of asthma by decade:

Decade	Drugs used
1960's	Aminophylline, Epinephrine, Ephedrine
1970's	Beta-agonists, Theophylline, 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 include gene therapy.

Medications are divided into 2 main categories:

Categories	Medications
Quick relief medications	1) Inhaled Short acting Beta-2 Agonists 2) Inhaled Anticholinergic 3) Systemic Corticosteroids
Long-term control medications	1) Inhaled Long-acting Beta-2 Agonists (LABA) 2) Topical (inhaled) Corticosteroids 3) Inhaled Cromolyn Na and Nedocromil 4) Oral Methylxanthines (Theophyllines) 5) Oral leukotriene modifiers (LTRA)

Beta-2 Adrenergic Agonists (short term & long term):

Information:	Molecular Actions:	Toxicity:
▪ Medication of choice for acute exacerbations ▪ Actively relax airway smooth muscles ▪ Inhibit release of mediators ▪ Enhance muco-ciliary activity ▪ Decrease vascular permeability ▪ Inhibit eosinophil activation	▪ Increase cAMP ▪ Activate protein kinase A ▪ Phosphorylate kinases ➔ All lead to decreased cytosolic Ca++ NOTE: Ca++ is responsible for contraction of smooth muscles, so increasing cAMP will decrease calcium.	▪ 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. ▪ Use of beta-2 Agonists is associated with increased risk of death

Epinephrine: (was used in the past, and still used nowadays)

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

(Epinephrine will raise the blood pressure and cause bronchodilation, so it'll relieve bronchial asthma)

Isoproterenol:

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

Type	Info	Drugs
Short acting beta-2 agonists	▪ **Only used on a p.r.n. basis (the medication is taken as needed only, no regular use)** ▪ Rapid onset: 3-5 minutes ▪ Maximal effect: 30-60 minutes ▪ Duration: 4-6 hours	▪ Albuterol (Salbutamol) ▪ Terbutaline ▪ Pirbuterol ▪ Metaproterenol ▪ Isoetharine
Long-acting beta-2 agonists (LABA)	▪ Long-acting inhaled bronchodilators: 12 hours ▪ Suppress night-time attacks ▪ Controller with steroids ▪ No tachyphylaxis (tolerance)	▪ Salmeterol ▪ Formoterol

Notes:

- Patients **homozygous for glycine at the B-16 locus of the β receptor** improved with regular use of albuterol or salmeterol.
- Patients **homozygous for arginine at the B-16 locus of the β receptor** (found in 16% of Caucasians and more frequently in blacks) deteriorated with regular use of albuterol or salmeterol.

Methylxanthines (long term):

➔ Drugs: Xanthine, Theophylline, Aminophylline, Theobromine, Caffeine

Information:	Molecular Actions:	Side effects:
▪ **CNS stimulants** ▪ Cardiovascular stimulants ▪ Oral and intravenous ▪ **Were the mainstay treatment (60s-70s)** ▪ **Low therapeutic index** ▪ Blood assay is a routine (drug monitoring is required) ▪ Optimal dosing is very difficult ▪ Half-life: 3-16 hours	▪ Phosphodiesterase inhibition ▪ Adenosine receptor antagonism ▪ Anti-inflammatory activity - Phosphodiesterase enzyme: it's the enzyme which breaks down cAMP. Recall that cAMP is important for dilatation and relaxation of smooth muscles. - Adenosine causes bronchoconstriction	▪ Cardiovascular stimulants; can cause arrhythmias. ▪ Nausea, GIT irritation, diarrhea ▪ Wide inter-individual variation in the rate of hepatic metabolism ▪ Food and drug interactions (erythromycin and ciprofloxacin)

Note: 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) and airway inflammatory infiltration.

Anticholinergic Agents (short term):

Atropine :

Information:	Side effects:
▪ 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 :

Information:	Side effects:
▪ Poorly absorbed from respiratory mucosa. ▪ Doesn't impair clearance of airway secretions. ▪ Metered dose inhaled and as a solution for nebulization. ▪ Mainly for COPD, not for asthma, because of slow onset (10-15 minutes) and low potency. **NOT USED FOR EMERGENCY** ▪ Might be very useful in special conditions (beta blocker-induced asthma, resistant attacks, cardiac patients)	▪ Causes minimal cardiac or central effects.

Anti-inflammatory agents and Alternative therapy:

- Corticosteroids
- Inhibitors of Mast Cell Degranulation
- Leukotriene Pathway Modifiers
- Immunomodulatory Agents

Corticosteroids (short & long term):

Information:	Actions:	Side effects:
▪ Inhibits the synthesis and release of chemical mediators (histamine, PGs and cytokines) ▪ Suppress the inflammatory cell influx and 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	➔ Highly lipophilic ▪ Binds to cytosolic receptors ▪ The drug-receptor complex enters the nucleus ▪ Decrease transcription of genes coding for pro inflammatory cytokines ▪ Takes several hours to days to work	**Local side effects:** ▪ Hoarseness of voice (dysphonia) ▪ Sore throat and cough ▪ Candida infection **Systemic side effects:** ▪ Osteoporosis ▪ Cataract ▪ Glaucoma ▪ Growth retardation ▪ Adrenal suppression ▪ CNS effects and behavioural disturbances ▪ Increased susceptibility to infections ▪ Teratogenicity

➔ Short term systemic use in severe refractory attacks.
➔ Long term use for "Steroid Dependent" asthma.

Type	Information	Drugs
Short term corticosteroids	▪ Systemic use ▪ Oral or injectable	▪ Cortisone ▪ Prednisolone ▪ Dexamethasone
Long term corticosteroids	▪ Taken by inhalation ▪ Aerosol treatment is the most effective way to avoid the systemic adverse effects	▪ Beclomethasone ▪ Trimacinolone ▪ Flunisolide ▪ Budensonide ▪ Fluticasone

Cromolyn Na and Nedocromil Na (long term):

*They're inhibitors of Mast Cell degranulation

-> Recall that Ag-Ab reaction occurs on the mast cells, and it causes the breakdown of mast cells releasing Histamine. Histamine is a bronchoconstrictor.

Information:	Actions:	Side effects:
▪ Inhibit the release of inflammatory mediators from mast cells **(Mast Cell stabilizers)** ▪ Prophylactic for mild to moderate asthma ▪ Not for acute asthma ▪ Regular use (4 times daily)	▪ Phosphorylates a cell membrane protein, so, mediators release is inhibited despite antigen-IgE interaction ▪ Might decrease Ca++ ▪ Might decrease neural pathways, plasma exudation and inflammation in general	▪ NO SIDE EFFECTS

Leukotriene Pathway modifiers (long term):

➔ Some information about leukotriene pathway:
- **This reaction is not an allergic response**, can be induced by many different chemicals (**tetrazine, FDC Color #5**), and does not involve IgE antibody response.
- 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

➔ Examples on leukotriene pathway modifiers:

Drugs	Information
Zileuton	▪ **Inhibitors of 5- Lipoxygenase enzyme** ▪ **Used for acute and chronic treatment** ▪ **Hepatotoxic** ▪ Used 4 times daily
Montelukast & Zafirlukast	▪ **Antagonists of Cysteinyl Leukotriene Receptors**

Immunomodulating Biotherapeutics:

Example: Omalizumab

Information:	Actions:
▪ It's a humanized monoclonal anti-IgE antibody raised in mice. ▪ Not recognized as foreign by human immune system. ▪ Given as IV or SC injections every 2-4 weeks	▪ 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 ▪ 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**

Therapy of Asthma:

General therapy of Asthma	Therapy of Status Asthmaticus	Possible future therapies
▪ Oxygen ▪ Hydration: Oral or Intravenous ▪ Expectorants ▪ Antimicrobials	▪ Oxygen. ▪ Inhaled short acting Beta-2 agonists. ▪ Oral or parenteral corticosteroids. ▪ Subcutaneous Beta-2 agonists. ▪ Inhaled Ipratropium bromide maybe effective in some patients. ▪ Epinephrine by subcutaneous injection	▪ **Macrolide (erythromycins) and antimicrobial therapies** for asthma caused by chronic airway infection with **Chlamydia Pneumonia or Mycoplasma Pneumonia**. ▪ Feeding **Lactobacillus caseii** to infants born to allergic parents reduced the rate of allergic dermatitis at age 2 years

THE END

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