ANTIASTHMATICS

This study material is exclusively for students of general medicine and stomatology in Pharmacology II course. It contains only basic notes of discussed topics, which should be completed with more details and actual information during practical courses to make a complete material for test or exam studies. Which means that without your own notes from the lesson this presentation IS NOT SUFFICIENT for proper preparation for neither tests in practicals nor the final exam.

Asthma bronchiale

= chronic respiratory tract inflammation

prevalence in CZ:

children 10-15 %, adults 3-5 %

Asthma bronchiale

- Constriction of bronchial smooth muscles
- Edematous changes on bronchial mucosa
- Increased mucus production and secretion

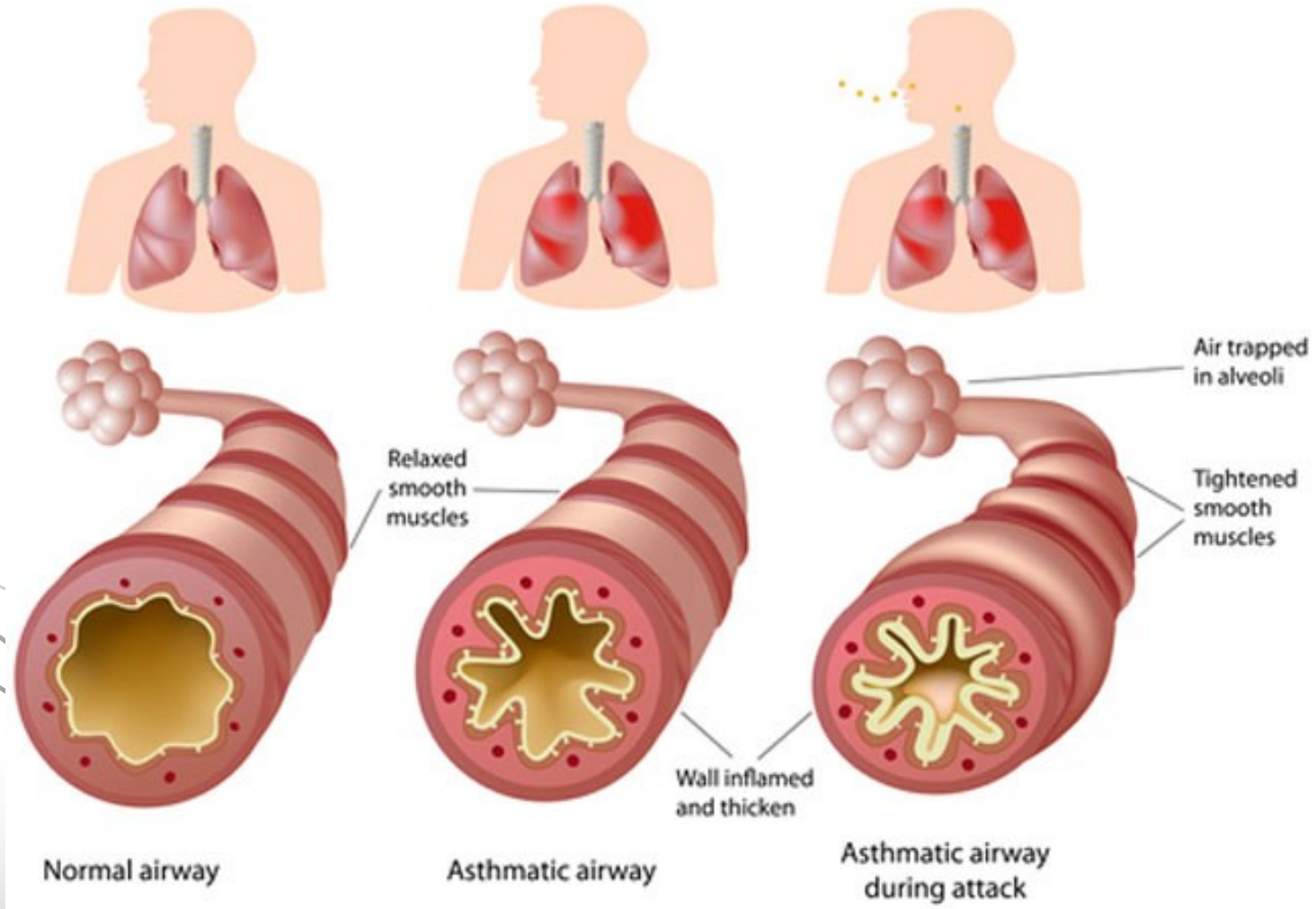
Symptoms

- **breathlessness** caused by bronchoconstriction, oedema, bronchial inflammation and mucus

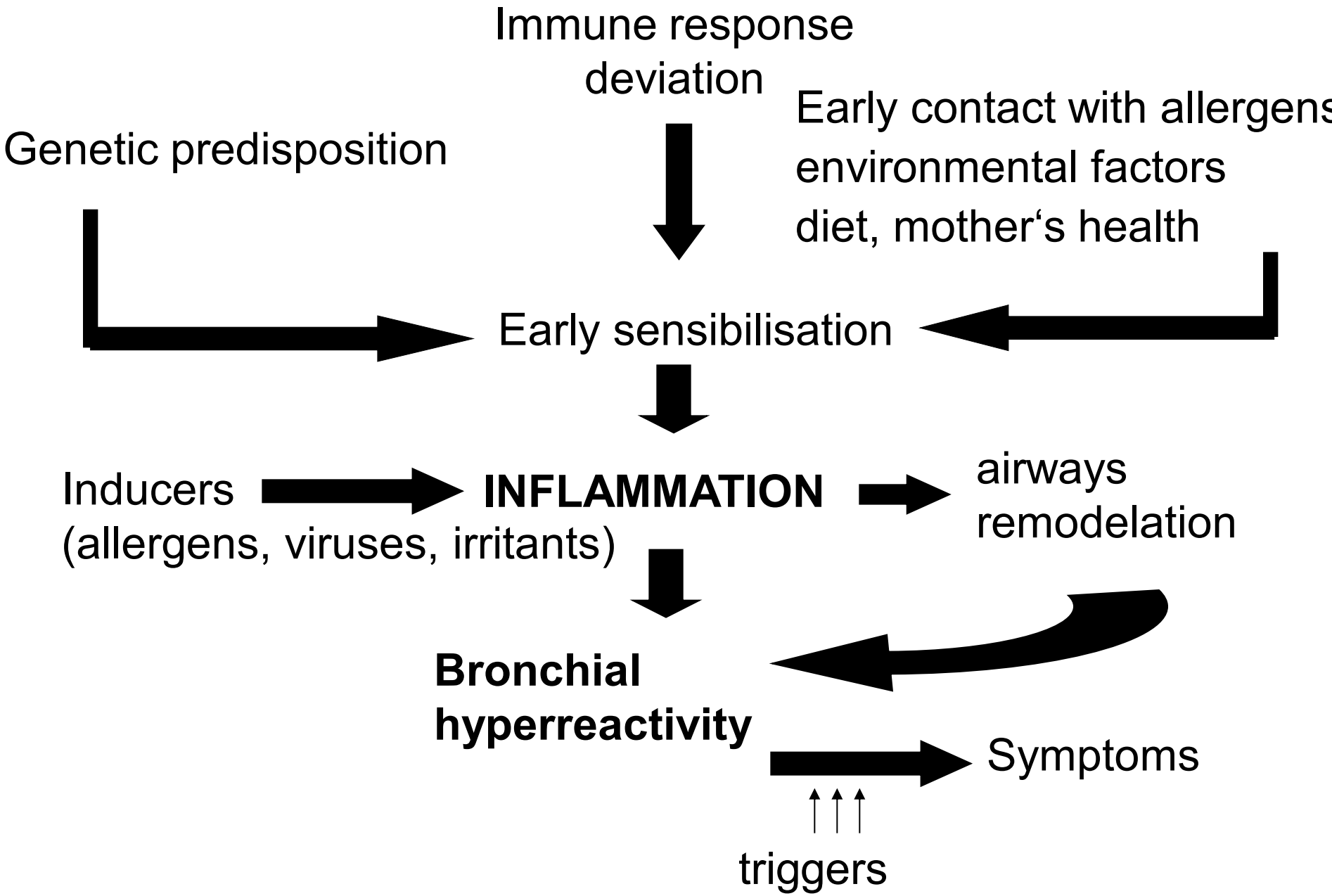
- difficult expiration, prolonged expiration, whistling, creaking.

- cough

Pathology of Asthma



Patophysiology



Diagnose

Anamnesis – personal, familiar

Clinical examinations - auscultation, signs of atopy, eosinophilia,

PEF – Peak Expiratory Flow

FEV – Forced Expired Volume

Laboratory tests- eosinophilia, IgE

Allergy testing

Asthma bronchiale classification

	allergic	non-allergic
inducer	contact with allergen	infection psychogennic phys. activity irritation aspirin
↑ of probability	young patients	older patients

Classification with regard to seriousness

- **Intermittent** – sign up to once a week, night symptoms up to twice a month, pulmonary function normal
- **Mild persistent**– signs no more than once daily, night symptoms up to twice a month, PEF at least 80 %
- **Moderate persistent**– signs once a day and are not permanent, night sign no more than once a week, PEF 60-80 %
- **Severe persistent**– permanent signs, daily, obstruction, PEF ≤ 60 %

Administration of antiasthmatics

- Peroral

- Injections

- **Inhalation**

  benefits: high drug concentration on the site of action

  fast onset of effect

  minimal penetration to systemic circulation = low risk of systemic AE

Inhalation preparation for antiasthmatics

- Aerosol dispensers – meter dose dispensers
- Aerosol dispenser + spacer – children elders
- Powder (spinhaler, dischaler, turbohaler)
- Nebulizer

Asthma bronchiale pharmacotherapy

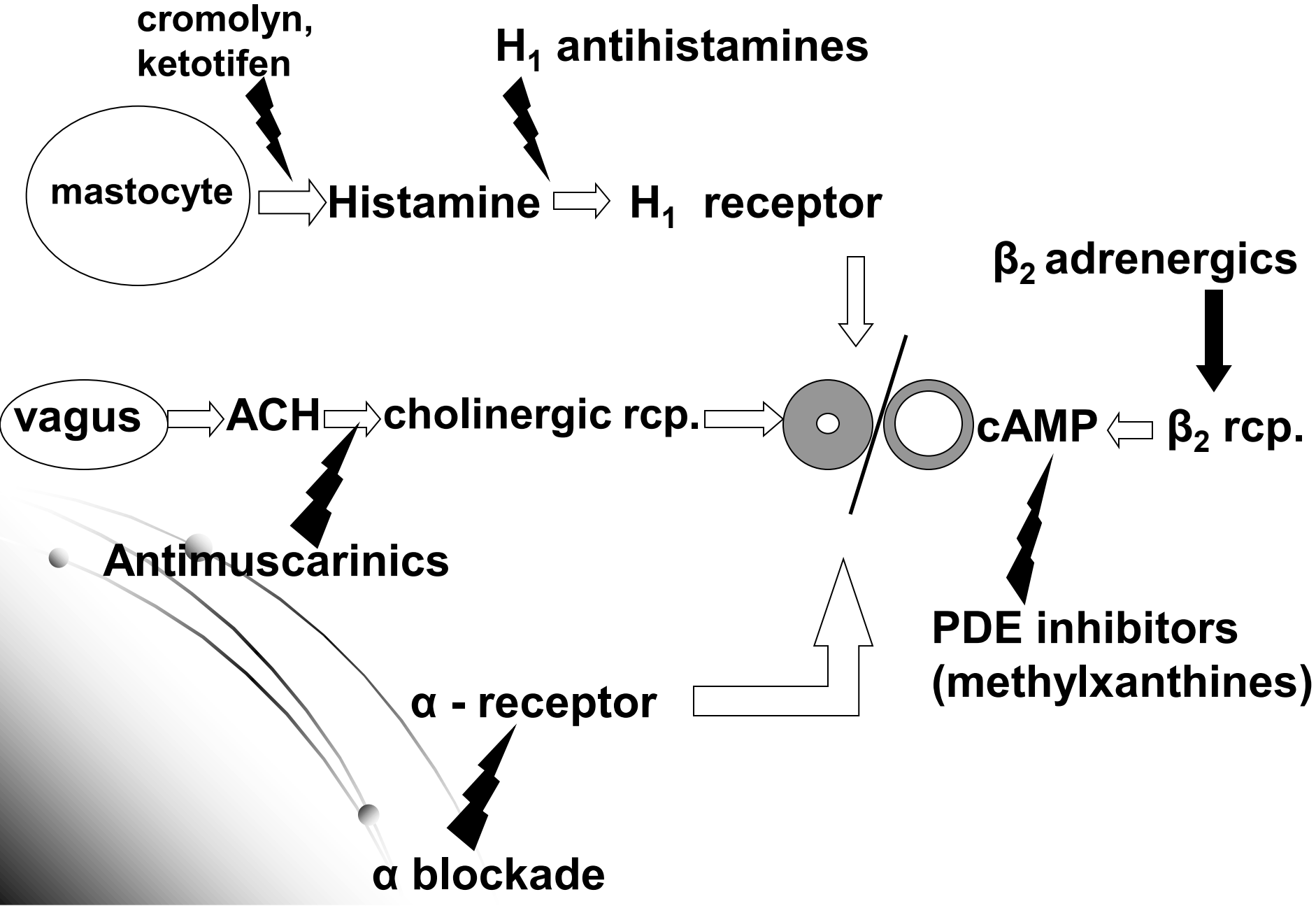
- Quick relief drugs – acute attack
- Long-term control medicines – between attacks

Pharmacotherapy

1. **Bronchodilators**
   - β-sympathomimetics
   - nonselective sympothomimetics
   - antimuscarinics
   - methylxanthines
2. Anti-inflammatory agents
   - Glucocorticoids
   - Immunoprophylactics
3. Adjuvant therapy and other drugs of respiratory system
   - Antileucotriens
     - leucotriens‘ receptors antagonists.
     - 5-LOX inhibitors
   - Antighistamines
   - Expectorants
   - Antitussives

- Hyposensibilisation
- Anti IgE monoclonal antibodies

Bronchodilators target sites on smooth muscle cells



1. Bronchodilators
β- sympathomimetics

- selective stimulation of β_2-Rc
- adenylyl cyclase stimulation → ↑cAMP → bronchial smooth muscles relaxation
- decrease in inflammation mediators from mastocytes
- increase in cilliar activity

1. Bronchodilators
β- sympathomimetics

- **Short-acting (max. 4 - 6 hrs.)**

  salbutamol

  fenoterol

  terbutaline

  hexoprenaline

1. Bronchodilators
β- sympathomimetics

- **Long- acting (12 hrs.)**

  prokaterol

  formoterol

  salmeterol

  clenbuterol

  bambuterol

1. Bronchodilators
β- sympathomimetics

- AE:

  nervousness, tremor, cephalgia, palpitation

  hypokalaemia

- CI:

  dysrhythmia, hypertension

  (pregnancy)

1. Bronchodilators

Nonselective sympathomimetics

epinephrine– in life-threatening situations

ephedrine

orciprenaline

More of AE

tachycardia, palpitation, dysrhythmia, hyper/hypo tension, insomnia

1. Bronchodilators Antimuscarinics

- for inhalation
- blocks cholinergic M receptors
- to increase the effect of β_2-sympathomimetics

ipratropium
tiotropium

atropine analogues, inhalation in combination with beta-mimetics – or administration after beta-mimetics

when combined with corticoids, then administered after them

- AE: dry mouth, urine retention, constipation
- CI: prostate hypertrophy, glaucoma, pregnancy

1. Bronchodilators Methylxanthines

- phosphodiesterase inhibitors → ↓ cAMP degradation → smooth muscle relaxation
- bronchodilators, cardiostimulants, diuretics

- retarded DDF (before going to bed)

  theophylline

  aminophylline

  ethophylline

1. Bronchodilators
Methylxanthines

adenosine receptor antagonists

(adenosine $\Rightarrow$ contraction, $\uparrow$His, LT, Pg)

More effects:

CNS stimulation; +chrono, +inotropic effect, $\downarrow$blood viscosity and hemoperfusion (pentoxiphillin)

gastric acid secretion increase

AE: similar to those of non-selective sympathomimetics

Pharmacotherapy

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   - antimuscarinics
   - methylxanthines
2. **Antiinflammatory agents**
   - Glucocorticoids
   - Immunoprophylactics
3. Adjuvant therapy and other drugs of respiratory system
   - Antileucotriens
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   - Antighistamines
   - Expectorants
   - Antitussives

- Hyposensibilisation
- Anti IgE monoclonal antibodies

2. Antiinflammatory agents Glucocorticoids

anti-inflammatory and immunosuppressant activity (PLA_2 inhibition)

- ↓ cytokines, prostaglandins and leukotrienes secretion
- ↓ lipolytic and proteolytic enzymes secretion
- ↓ endothelial permeability

2. Antiinflammatory agents Glucocorticoids

- **block cell migration and decrease bronchial hypereactivity, suppress oedema**
- **block chronic ireversible changes development (bronchial smooth muscles hypertrofia and hyperplasia, subendothelial fibrosis and thickening of mucous basal membrane)**
- **increase sensivity of β adrenergic receptors to beta mimetics**

2. Antiinflammatory agents Glucocorticoids

Orally or inhalation

- Inhalation

  beclomethasone

  budesonide

  fluticasone

  flunisolide

  dexamethasone

  mometason

  ciclesonide

AE: hoarseness, cough, oral candidosis (wash out mouth after use)

2. Antiinflammatory agents Glucocorticoids

- Orally

when inhalation are not sufficient

in challenge doses which are gradually decreased

prednisone

triamcinolone

betamethasone

2. Antiinflammatory agents Glucocorticoids

AE:

- candidosis, risk of systemic adverse effects

- systemic: Cushing‘s sy., DM, immunosuppresion, ostoporosis, hypertension, gastroduodenal ulcers...

2. Antiinflammatory agents Immunoprophylactics

- mast cells membrane stabilizers
- inhibit histamine release
- influence on lymphocytes

in mild forms of asthma
prevention of asthma attacks, maintenance therapy

cromones (cromoglycate, nedocromil)
ketotifen (H1 antagonist, anti-Ach effect)

CI: 1. trimester of pregnancy

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3. Adjuvant therapy

Antileucotriens

for mild forms of asthma

in serious asthma in combination with corticoids

a) leucotrien receptor antagonists

montelukast

zafirlukast

b) 5-lipoxigenase inhibitors(5-LOXi)

zileuton

piriprost

docebenone

c) both effects (antag. rcp. + i 5-LOX)

tenidap

3. Adjuvant therapy Antihistamines

2nd generation antihistamines with minimal sedative and arrhythmogenic effects

desloratadine

levocetirizine

fexofenadine

ketotifen

3. Adjuvant therapy Expectorants

- Secretolytics

bronchial gland stimulation = liquid mucus

ammonium chloride

potassium iodide

saponines – *Primula, Verbascum*

3. Adjuvant therapy Expectorants

- Mucolytics- decrease of mucus viscosity

  N-acetylcysteine

  carbocysteine

  ambroxol

  bromhexine (pro-drug)

  erdosteine

3. Adjuvant therapy Expectorants

- Secretomotorics

increase cilliar activity

essential oils: oleum eucalypti, o. menthae piperitae

bromhexine (pro-drug)

ambroxol

Others

guaifenesine

emetine

3. Adjuvant therapy
Antitussives

Cough = reflexive activity produced to release or clean up airways

- symptomatic therapy of irritating and exhausting cough
- do not combine with expectorants, namely secretomotorics for antagonistic effects

3. Adjuvant therapy
Codiene antitussives

- Block of cough center

  codein

  pholcodine

  ethylmorphine

  dextrometorphan

  levopropoxyphen

AE: respiratory center suppression → not for children!

3. Adjuvant therapy
Non-codeine antitussives - peripheral

- Block of sensitive neurons in submucosa

  dropropizine

  bezonatate

- Block of afferent pathways

  prenoxdiazine

3. Adjuvant therapy
Non-codeine antitussives - central

- Block of cough cetre, but do not suppress respiratory center

  butamirate

  (clobutinol – *withdrawn!!!)*

- Block of efferent pathways

  myorelaxants

  ganglioplegics

I: surgery

Anti IgE monoclonal antibodies

Omalizumab: monoclonal antibody used in bronchial asthma, that was unambiguously caused by IgE.

Mechanism of action: it binds to IgE, which decreases amount of circulating IgE and thus IgE can not bind to their specific receptors and trigger the allergic reaction.

It is administered subcutaneously.

Intended for therapy of severe persisting allergic bronchial asthma, that can not be controlled with high doses of inhalational glucocorticoids and during therapy with long-term acting inhalational β_2-sympatomimetics.

Disadvantage: high price.

THC ?

Two independent groups of investigators demonstrated a short-term bronchodilator response in healthy male volunteers to inhalation of the smoke of marijuana in concentrations of 1.0% to 2.6% $^{\Delta 9}$THC, that was not seen after inhalation of placebo.

The bronchodilator rresponse to smoked marijuana was of greater magnitude than that observed after administration of a nebulized β-agonist.

→ THC (ane other CB_1 receptor agonist) can have local bronchodilator effects in the airway through stimulation of CB_1 receptors on efferent vagal nerve endings, leading to a parasympatholytic effect.

Perspective use for athma therapy.

!!! CAVE: THC in form of marihuana smoke: pulmonary toxicity

risk of lung, neck and head cancer

Ziment I., Tashkin DPT (2000): Alternative medicine for allergy and asthma. *Journal of Allergy and Clinical Immunology*, 106, 603-614.