

# **Drugs used in diseases characterized by bronchial obstruction**

M U N I

# Bronchial asthma

M E D

chronic inflammatory disease of airways  
affecting 300 million people all across the globe  
prevalence in CZ: 8 %, in children over 10 %

## Characteristics:

bronchial hyper-reactivity  
obstruction (often reversible)  
inflammation

## Symptoms:

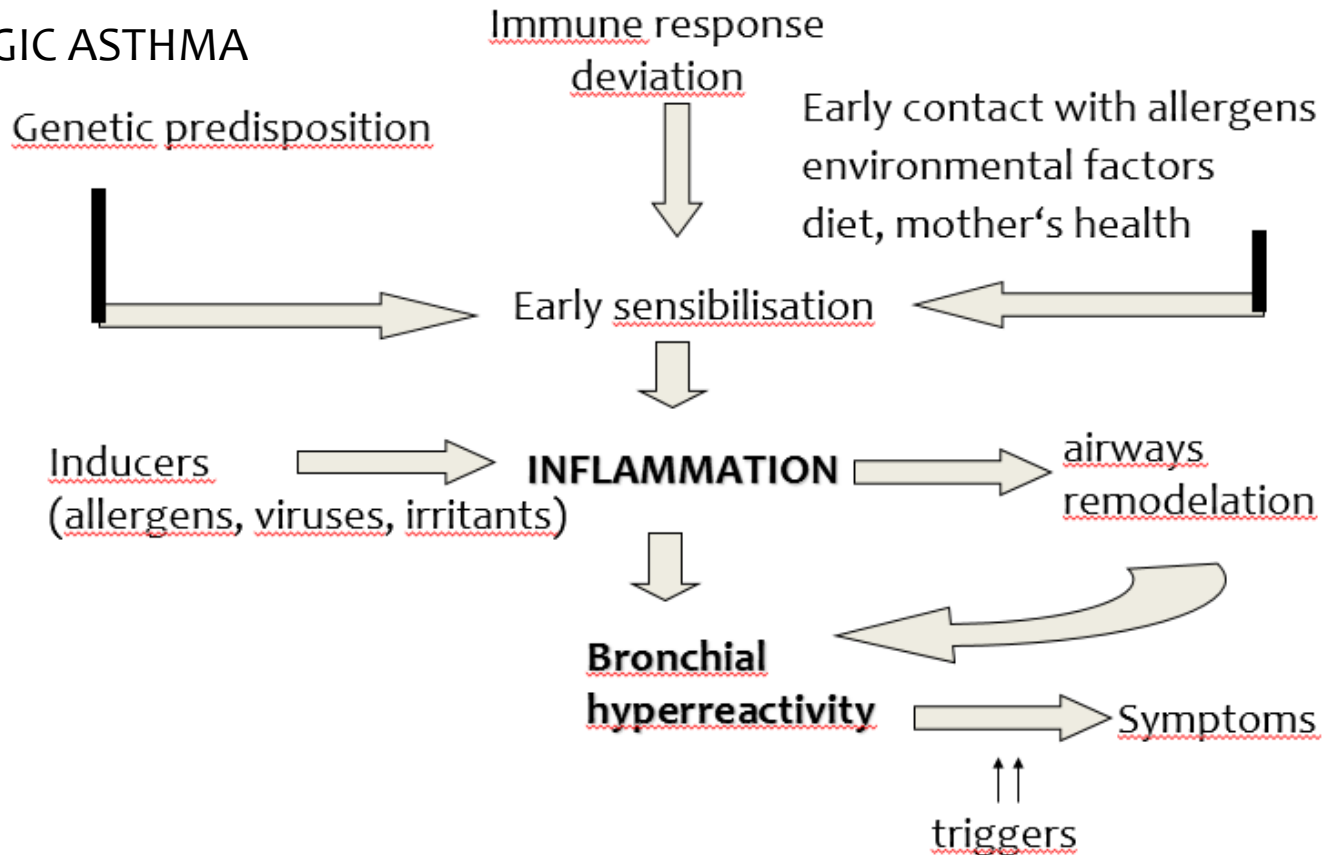
**shortness of breath** (bronchoconstriction, mucous plug,  
oedema, airway remodeling due to the inflammation)

difficult and prolonged **expiration** → wheezing, whistling

**cough** (especially at night or in early morning)

# Bronchial asthma

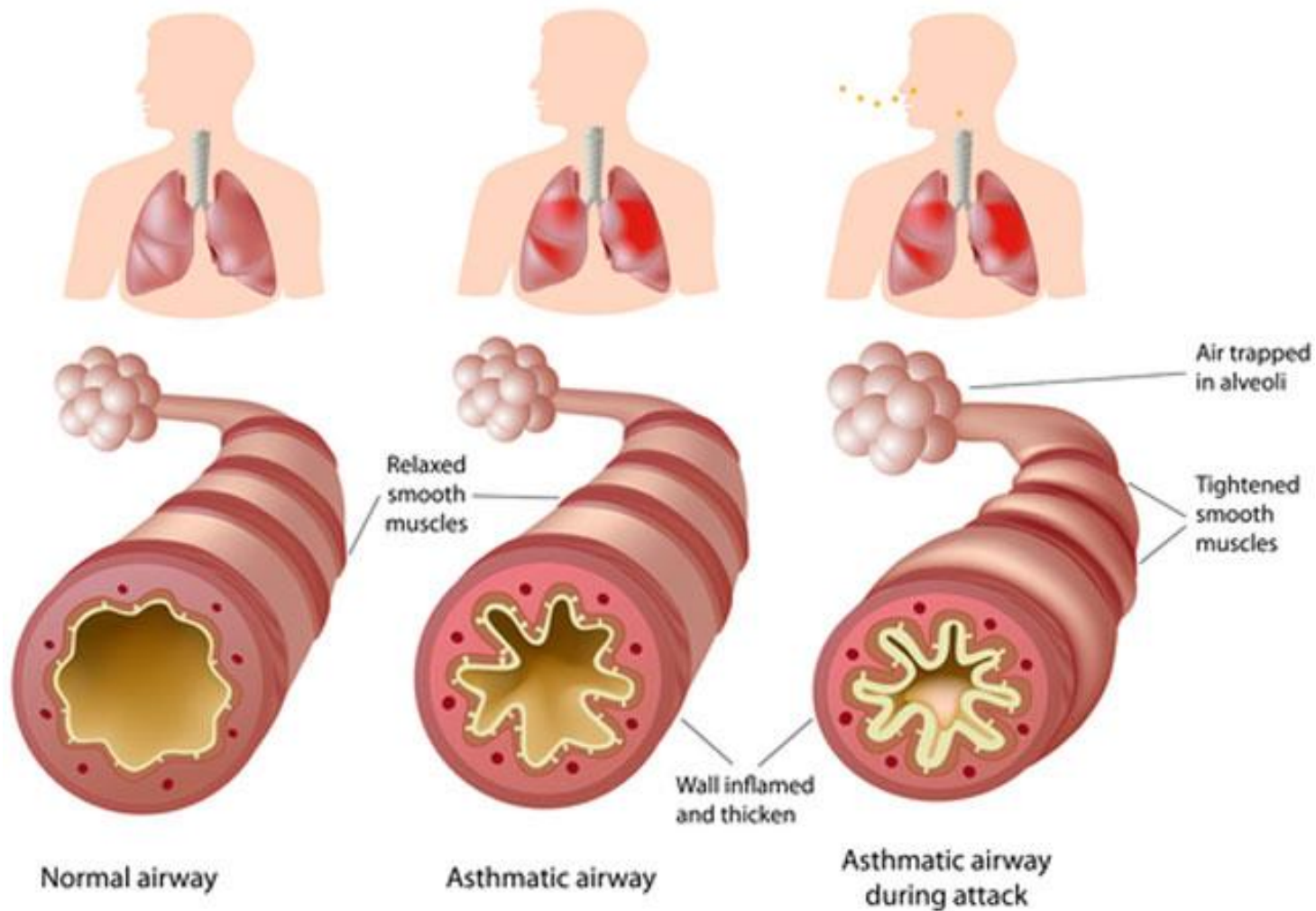
## ALERGIC ASTHMA



## NON-ALERGIC ASTHMA

- allergy not present
- exercise-induced, aspirin-sensitive, infectious, work-related, endogenous

## Pathology of Asthma



# Diagnose

Anamnesis – personal, familiar

Clinical examinations - auscultation, signs of atopy, eosinophilia,

PEF – Peak Expiratory Flow

FEV 1 – Forced Expired Volume in one second

Laboratory tests- eosinophilia, IgE

Allergy testing

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## 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  $\leq$  60 %

# Management of asthma

the disease itself cannot be fully treated, the goal is to keep asthma under control

## Goals:

- minimalize both acute and chronic symptoms
- reduction of exacerbations (lessen SABA administration)
- improvement of the quality of life (physical activity)
- avoid adverse effects of the treatment

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# **Chronic obstructive pulmonary disease (COPD)**

affecting 600 million people all across the globe  
prevalence: 8 %

risk factors: smoking, polluted air, dust and chemical vapors  
at workplace, genetic predisposition

## **Characteristics:**

chronic inflammation caused and maintained by long-term  
exposure to harmful agents (irritating gases and particles)  
poorly reversible, progressing bronchial obstruction  
production of mucus

## **Symptoms:**

**cough** (usually whole day, hardly ever only during night)  
**expectoration**  
**shortness of breath**



# Management of COPD

we can only slow the progression  
reduction of risk factors is necessary (mainly top quit  
smoking)

## **Goals:**

symptom reduction

improvement in physical condition and overall  
health state

prevention of complications and exacerbations

# Administration

oral, parenteral (injections, infusions)

## inhalation

- local administration, high drug concentration at the site of action
  - fast onset of the effect
- minimal penetration to systemic circulation → ↓ risk of side effects

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## Drugs used in diseases characterized by bronchial obstruction

### BRONCHODILATORS

- $\beta_2$  sympathomimetics
  - parasympatholytics
  - glucocorticoids
  - methylxanthines
  - roflumilast (COPD only)
  - antileukotrienes
  - immunoprophylactics
  - monoclonal antibodies
- } asthma only
- noselective sympathomimetics (epinephrine, life-saving medication)
  - adjuvant medication (antitussics, drugs facilitating expectoration)

# $\beta_2$ sympathomimetics

**MoA:** selective  $\beta_2$  stimulants

- inhibition of mediator release from mast cells + stimulation of ciliary beat frequency
- mostly **inhaled**, may be also given orally (mainly in kids)
- not completely selective in their binding to  $\beta$  receptors  
long-term use = down-regulation of receptors

# $\beta_2$ sympathomimetics

Indication: **asthma**, COPD

**AE:** nervousness, tremor, cephalgia, palpitation,  
hypokalemia (mainly when given orally)

**CI:** hypertension, dysrhythmia, pregnancy

# $\beta_2$ sympatomimetika

**Short-acting = SABA (also rapid-acting = RABA)**  
fast onset of effect, which lasts 4 – 6 hours, inhalation

salbutamol

fenoterol

**Long-acting = LABA**  
effect lasts for up to 12 hours, inhaled or administered orally

salmeterol

clenbuterol

formoterol (RABA)

indakaterol (U-LABA)

vilanterol (U-LABA)

# M U N I M E D

## Parasympatholytics

**MoA:** competitive antagonism of M receptors

- in a form of inhalation

- can be combined with  $\beta_2$ -sympathomimetics or glucocorticoids

**Indication: COPD, asthma**

**AE:** if entering the systemic circulation (low risk, they contain quaternary nitrogen in their structure) – anticholinergic effects

**CI:** glaucoma, prostate hypertrophy, pregnancy

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# Parasympatholytics

## ipratropium

- used in asthma as well – in patients resistant to  $\beta_2$  sympathomimetic treatment (approx. 1/6 of patients)  
short acting (SAMA)

**acclidinium (LAMA)**

**tiotropium (U-LAMA)**

**glykopyrronium-bromide (U-LAMA)**

**umeclidinium (U-LAMA)**

COPD  
only



# Glucocorticoids

**MoA:** inhibition of phospholipase A2  
by lipocortin

## Effects I:

↓ cytokine, PG a LT secretion

↓ lipolytic and proteolytic enzyme secretion

↓ endothelial permeability

block of cell migration

↓ bronchial hyperreactivity,

# Glucocorticoids

## Effects II:

reduction of edema

prevention of chronic irreversible changes  
(hypertrophy and hyperplasia of bronchial smooth  
muscles, subendothelial fibrosis and thickening of  
mucous basal membrane)

increase in sensitivity of  $\beta_2$  adrenergic receptors to  $\beta_2$ -  
SM

# MoA at the cellular level

glucocorticoid + cytoplasma receptor



↑ production of specific mRNA



↑ production of some proteins (lipocortins)

# MoA at the cellular level

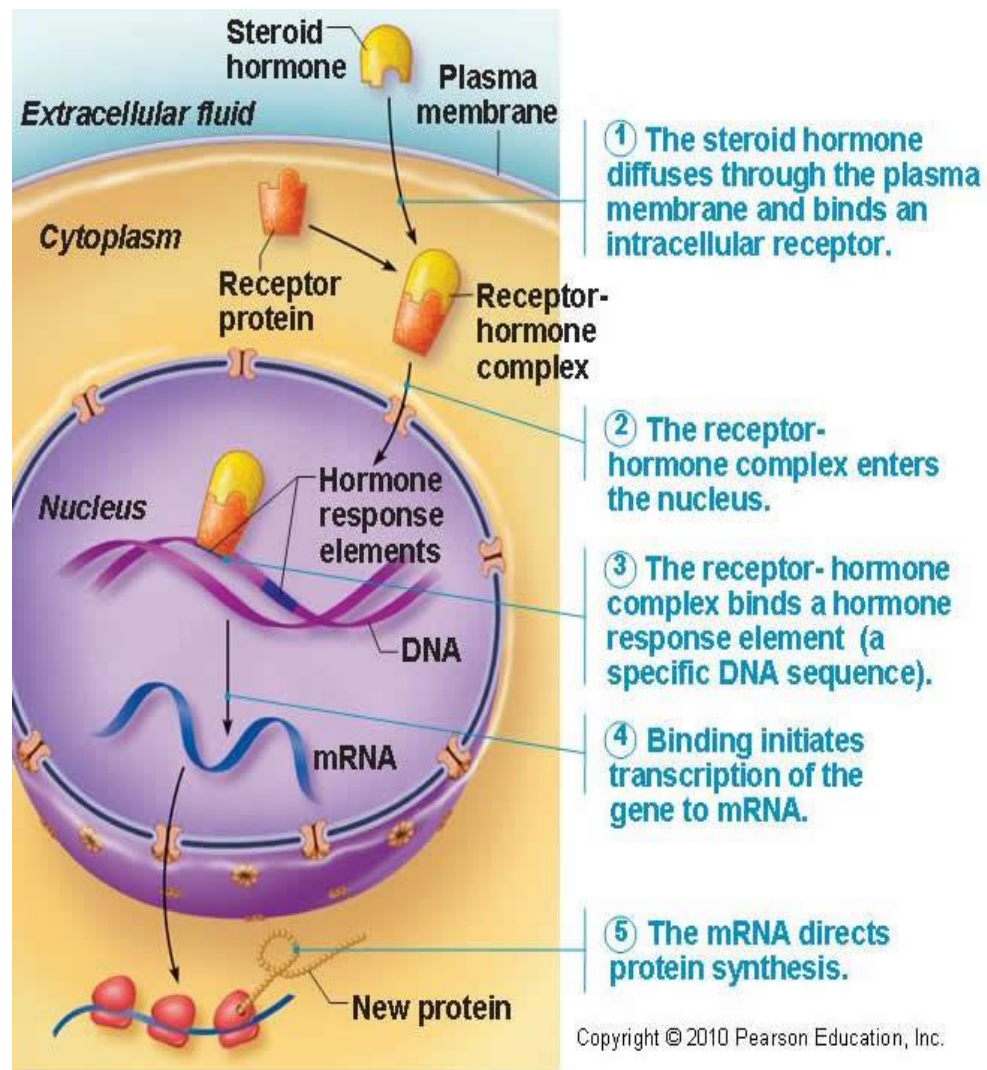
After entering the cell they bind to specific receptors in cytoplasm causing change of conformation = activation of receptors

Complexes of corticoid + receptor are transported to cell nucleus and bind to DNA elements.

The result is increased transcription of genes either inducing or inhibiting synthesis of other proteins

GLC receptors are present in all tissues!!!

Proteins called **lipocortins** are able to suppress phospholipase A



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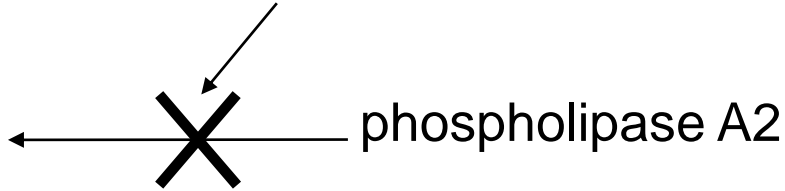
# Antiinflammatory effect of GC

AA cascade inhibition

**glucocorticoids**

membrane phospholipids

lipocortin



arachidonic acid

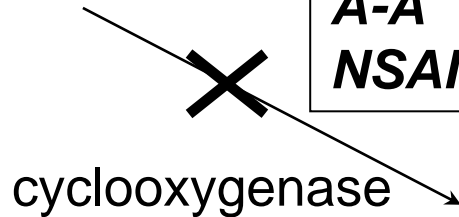
**Inh. 5-LOX**



LEUKOTRIENS

Mobilization of fagocytosis  
Changes in vessels permeability  
Inflammation

**A-A NSAIDs**



PROSTAGLANDINE  
PROSTACYCLINES  
TROMBOXANES

inflammation

# Glucocorticoids

## given by inhalation

lower risk of systemic adverse effects

AE: affected vocal cords – croaky voice, oral **candidiasis (thrush)**

**beclomethasone**

**budesonide**

**fluticasone**

**ciclesonide**

**mometasone**

## systemic administration

orally, via injection – acute conditions, doses are gradually decreased, in severe persistent asthma – if nothing else is effective

**prednisone**

**triamcinolone**

**hydrocortisone (injection)**

# M U N I M E D

## Methylxanthines

**MoA:** phosphodiesterase 1 – 4 inhibitors  
adenosine receptors antagonists

sustained-release drug forms

### Effects:

- bronchodilatation
- cardiostimulation (+chrono, +inotropic eff. )
- diuretic eff.
- CNS and respiratory center stimulation
- 23– stimulation of hydrochloric acid secretion

# Methylxanthines

## Effects:

- substrates of CYP450 – be cautious if patient is a smoker!

**CI:** pregnancy, epilepsy, cardiovascular disease

**AE:** tachycardia, palpitations, sleeplessness



**M U N I**

# **Methylxanthines**

**M E D**

## **theophylline**

- combination therapy with  $\beta_2$  SM is convenient

- becoming obsolete, therapeutic drug monitoring needed

- variable pharmacokinetics, low therapeutic index

## **aminophylline**

- a complex of theophylline and ethylenediamine (better solubility)

- COPD, emphysema

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# roflumilast

selective long-acting inhibitor of phosphodiesterase 4

reduces the inflammation in bronchi in COPD

# Antileukotrienes

**MoA:** antagonism of LT-receptors / inhibition of lipoxygenase

## **LT receptor antagonists:**

treatment of persisting asthma, allows lowering of glucocorticoid dose  
1-2x a day, orally

**montelukast**

## **Inhibitors of LOX:**

need for frequent application  
not registered in CZ (**zileuton** – USA)

# M U N I M E D

## Immunoprophylactics (mast cells stabilizers)

**MoA:** stabilisation of mast cell membrane  $\rightarrow$   $\downarrow$   $\text{Ca}^{2+}$  influx  $\rightarrow$   $\downarrow$  degranulation of mast cells and thereby  $\downarrow$  histamine release  
influence on lymphocyte function

prevention of asthma attack, they **do not affect already present bronchospasm**

**Use:** as preventive, long-term, maintenance therapy – mild and moderate asthma

when combined with other antiasthmatics, they allow lowering of their dose

**Cl:** pregnancy (1. trimester)

**nedokromil, ketotifen (H1 antihistamine), cromoglycate**

# Monoclonal antibodies

**Anti-IgE**

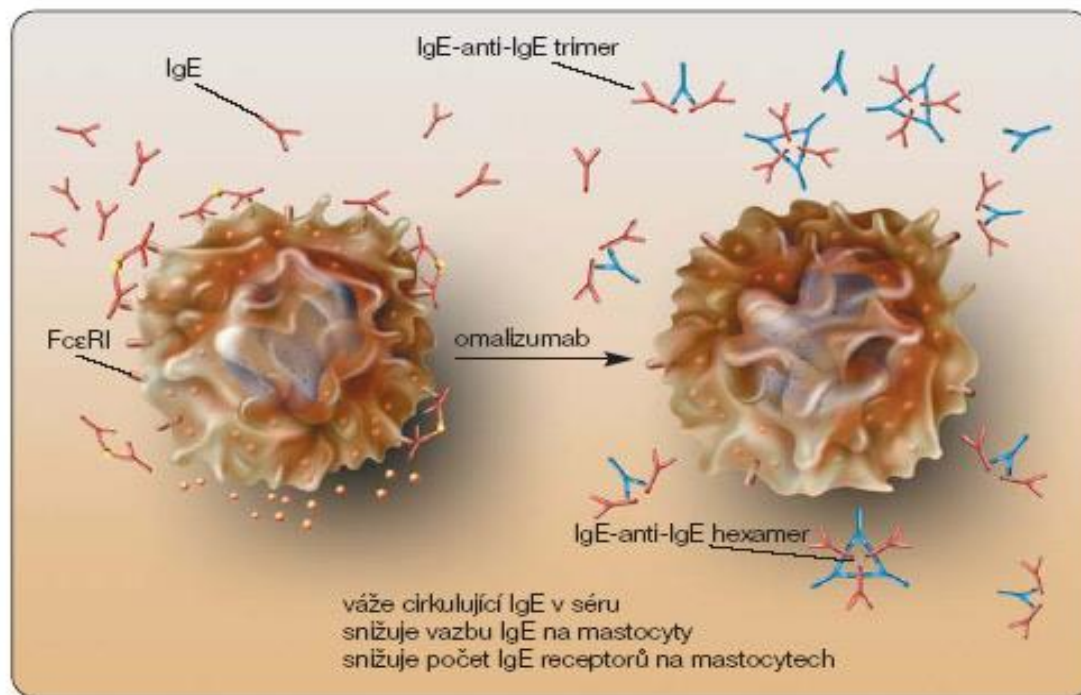
**omalizumab**

antibodies against a part of IgE, which binds to mast cells

Indication: severe persistent allergic asthma, which cannot be otherwise controlled

administered subcutaneously in specialized centres only

# Anti-IgE omalizumab



Obr. 3 Mechanismus působení omalizumabu

# Monoclonal antibodies

## Anti-IL-5

**mepolizumab, reslizumab**

add-on treatment for severe refractory eosinophilic  
asthma in adult patients

## Other options

### Bronchial thermoplasty

- bronchoscopic procedure, during which a therapeutic radiofrequency energy is delivered to the airway wall, resulting in reduction of smooth muscle cells

### Allergen immunotherapy

- induces tolerance to the triggering allergen



# M U N I M E D

## Devices for inhaled medications

**MDI** = metered dose inhalers  
drugs as solutions, propellants

**BAI** = breath-actuated inhalers

**DPI** = dry powder inhalers  
spinhaler, diskhaler, turbohaler

**nebulizers** (liquid → aerosol)

# M U N I M E D

## Devices for inhaled medications

spacers for children and elderly

patient must be educated how to use their inhaler  
→ up to 41 % of patients use incorrect technique

inhalers often combine two drugs (bronchodilator + glucocorticoid  
or two bronchodilators)

(„**fixed combination**“), SABA/LABA + LAMA called „**dual combination**“

# MUNI MED



**M U N I**  
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**Adjuvant medication in diseases characterized  
by bronchial obstruction and  
another drugs affecting respiratory system**

antitussives

drugs facilitating expectoration

H<sub>1</sub> antihistamines (mainly II. a III. generation)