

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:

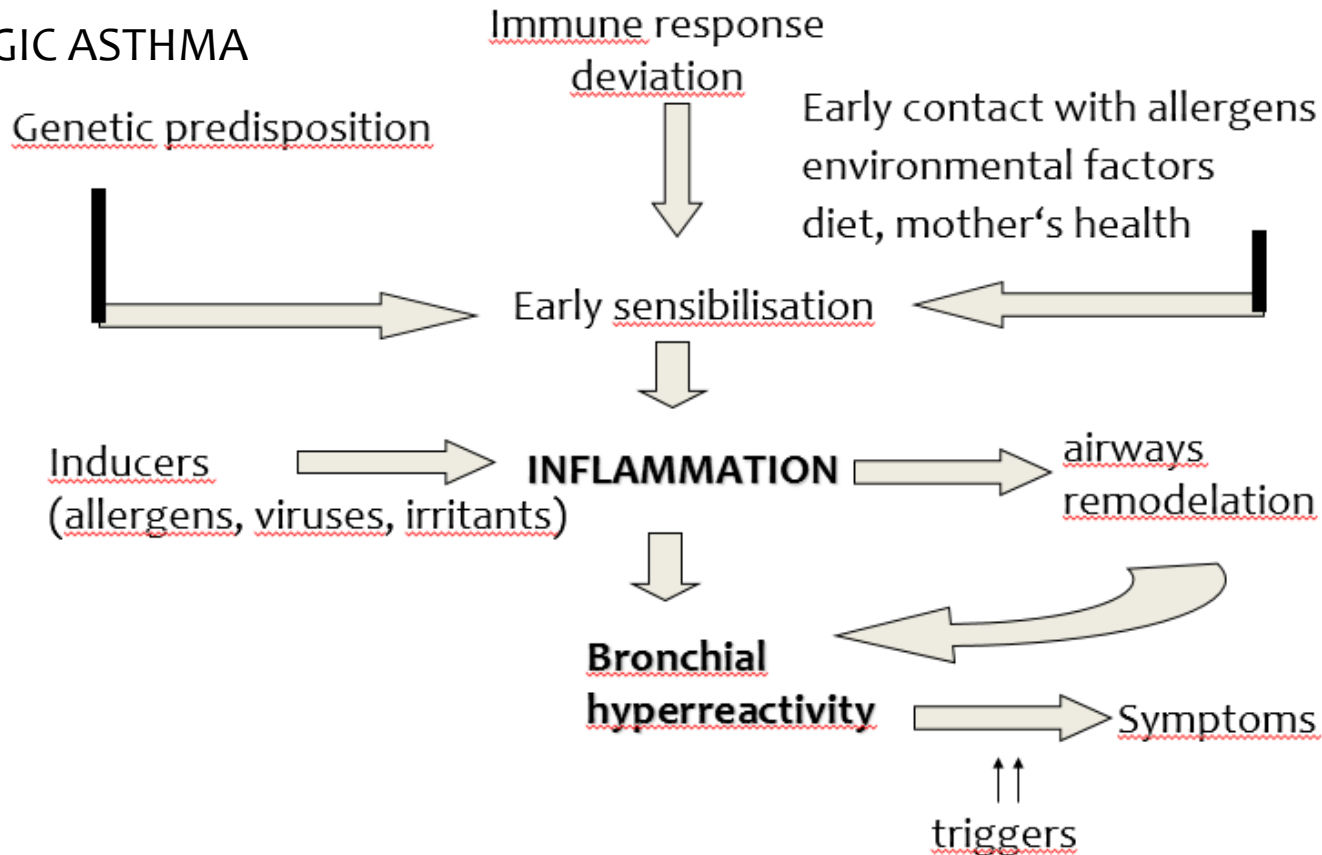
shortness of breath (bronchoconstriction, mucous plug,
oedema, airway remodeling due to the inflammation)

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

cough (especially at night or in early morning)

Bronchial asthma

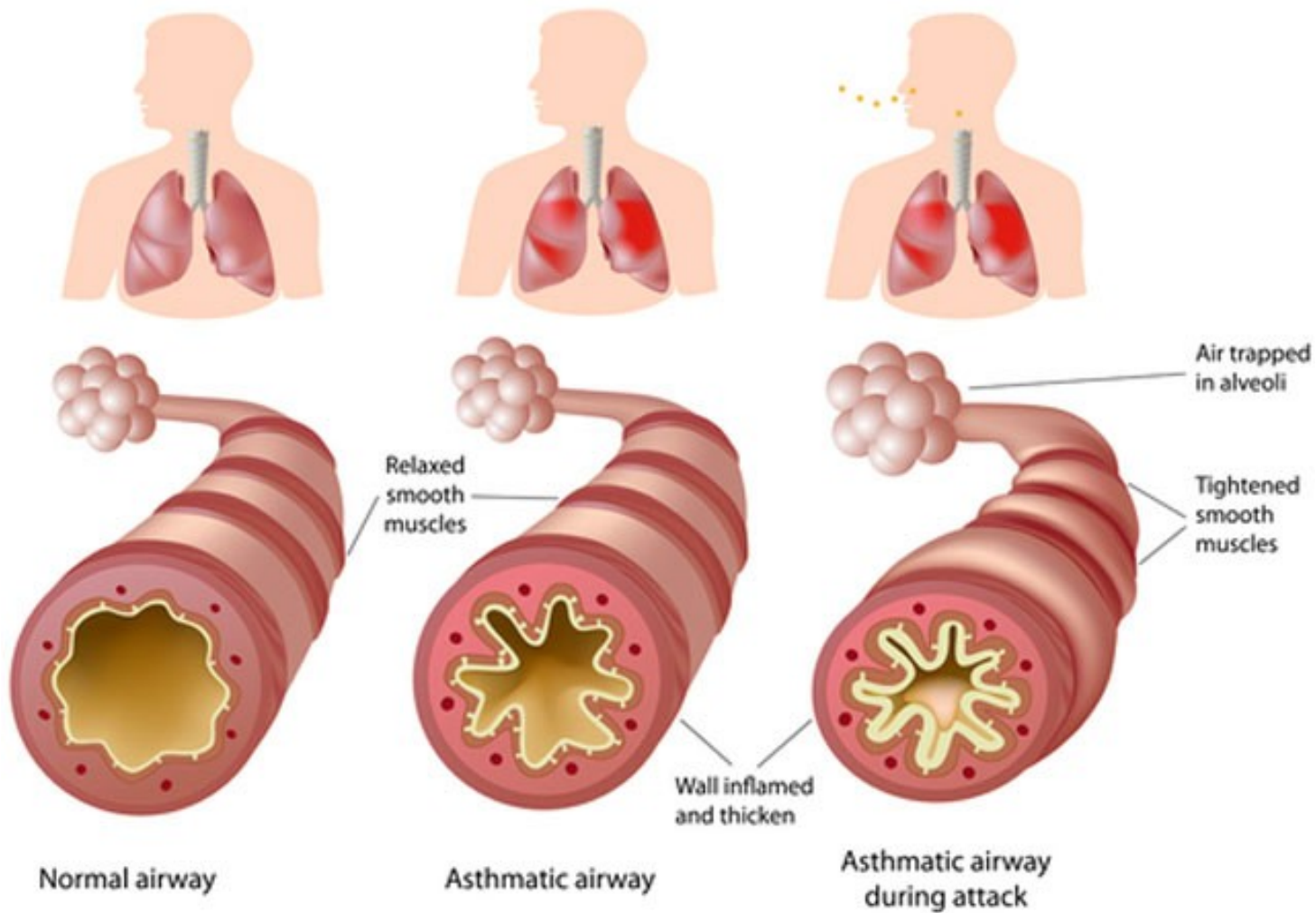
ALERGIC ASTHMA



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

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

- β_2 sympathomimetics
 - parasympatholytics
 - glucocorticoids
 - methylxanthines
 - roflumilast (COPD only)
 - antileukotrienes
 - immunoprophylactics
 - monoclonal antibodies
 - noselective sympathomimetics (epinephrine, life-saving medication)
 - adjuvant medication (antitussics, drugs facilitating expectoration)
-
- asthma only

β_2 sympathomimetics

MoA: selective β_2 stimulants

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

β_2 sympathomimetics

Indication: **asthma**, COPD

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

CI: hypertension, dysrhythmia, pregnancy

β_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)

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Parasympatholytics

MoA: competitive antagonism of M receptors

- in a form of inhalation
- can be combined with β_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

Parasympatholytics

ipratropium

- used in asthma as well – in patients resistant to β_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 β_2 adrenergic receptors to β_2 -
SM

MoA at the cellular level

glucocorticoid + cytoplasma receptor



↑ production of specific mRNA



↑ production of some proteins (lipocortins)

MoA at the cellular level

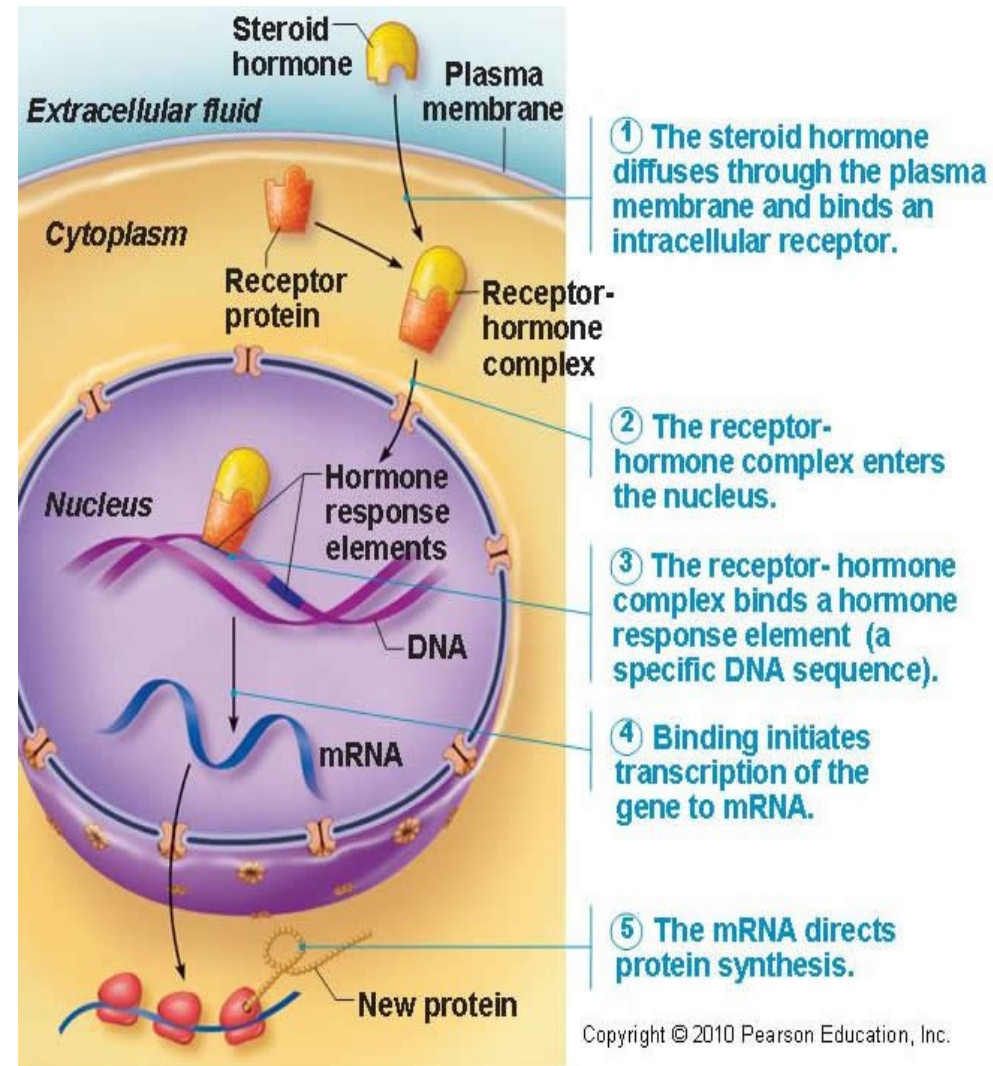
After entering the cell they bind to specific receptors in cytoplasm causing change of conformation = activation of receptors

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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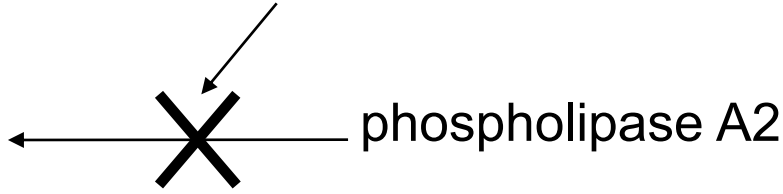
Antiinflammatory effect of GC

AA cascade inhibition

glucocorticoids

membrane phospholipids

lipocortin



arachidonic acid

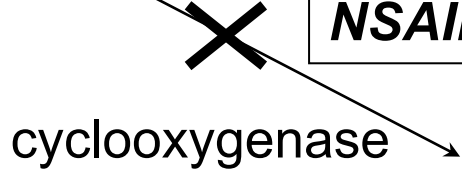
Inh. 5-LOX



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)

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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
- 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

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Methylxanthines

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theophylline

- combination therapy with β_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)

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Immunoprophylactics (mast cells stabilizers)

MoA: stabilisation of mast cell membrane → ↓ Ca²⁺ influx → ↓ degranulation of mast cells and thereby ↓ 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

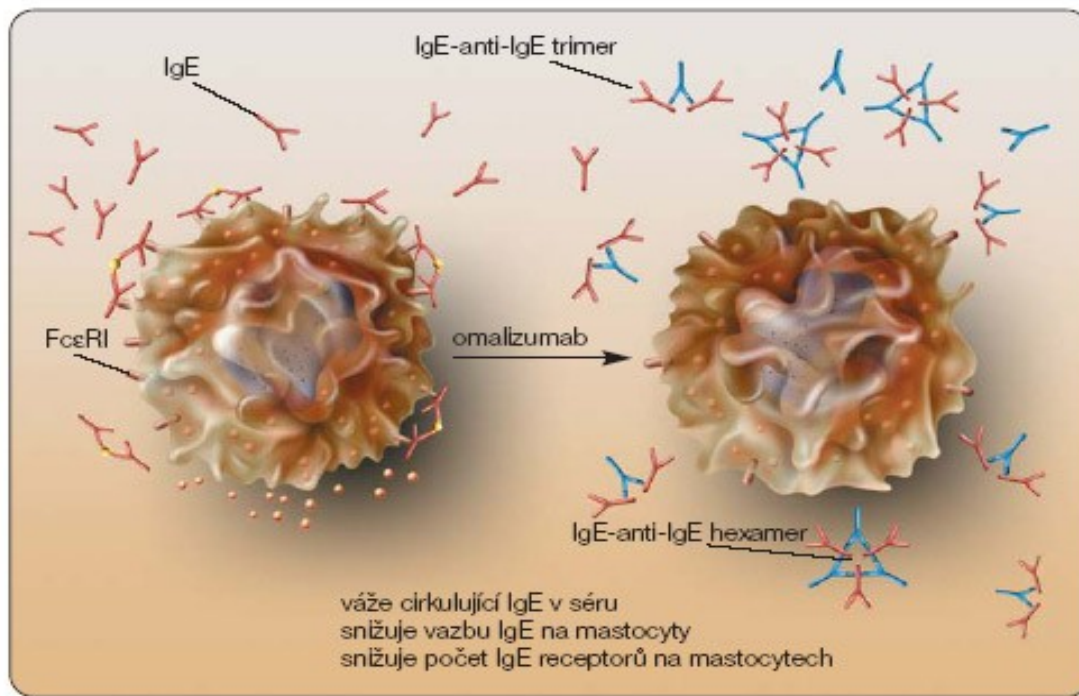
omalizumab

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

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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)

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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)

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**Adjuvant medication in diseases characterized
by bronchial obstruction and
another drugs affecting respiratory system**

antitussives

drugs facilitating expectoration

H₁ antihistamines (mainly II. a III. generation)