Drugs used to treat bronchial asthma

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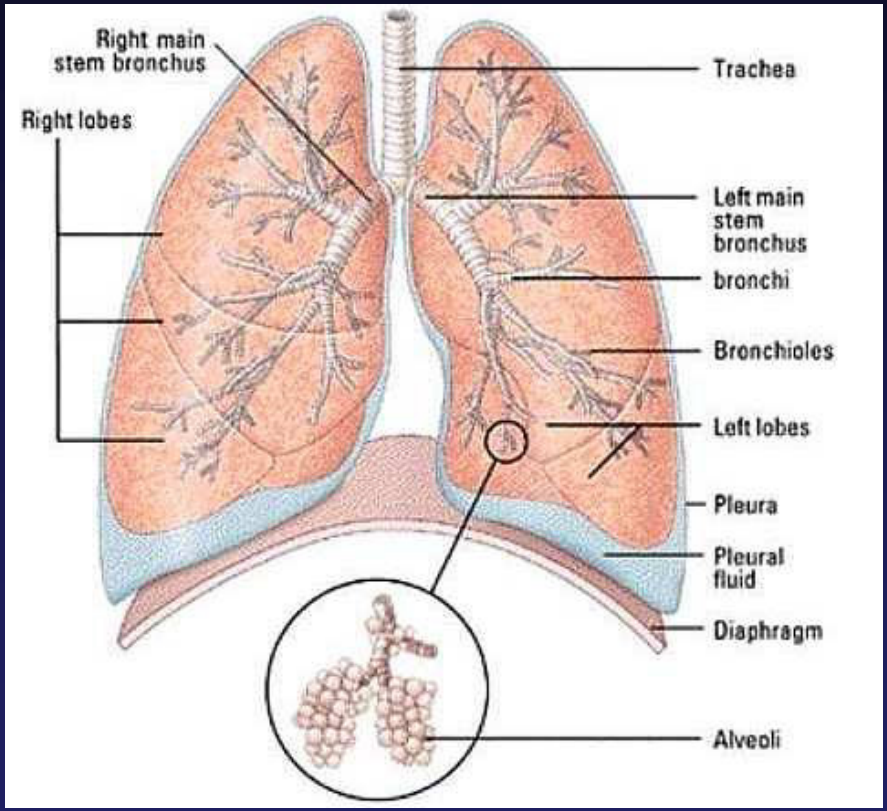
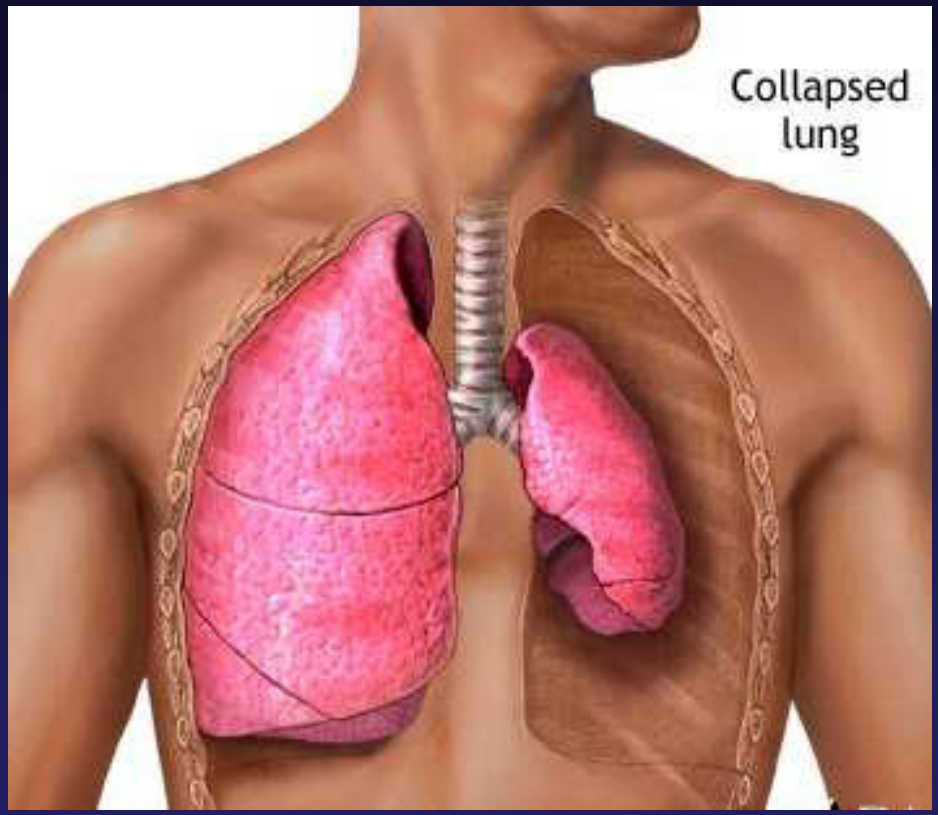
Structure of the lung and airways



Airways



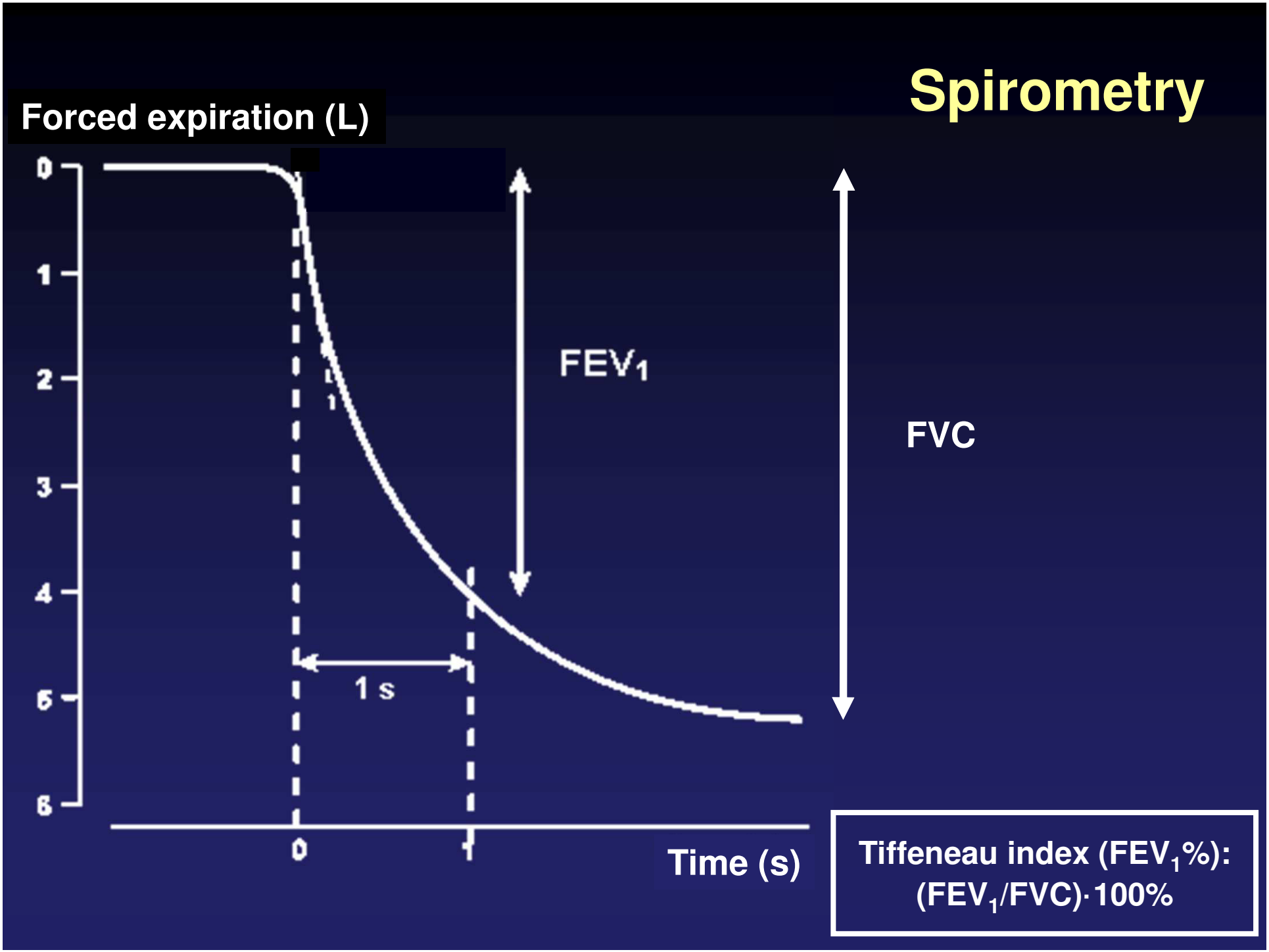
Left-sided pneumothorax (PTX)

Airflow limitations of mechanical origin

- **Obstructive** (increase in the airway resistance)
  - Upper respiratory tract obstruction (e.g. subglottic laryngitis)
  - Lower respiratory tract obstruction
    - Bronchitis and bronchiolitis
    - Pulmonary emphysema

    } **COPD**
    - Bronchial asthma (**BA**)
- **Restrictive** (decrease in the respiratory surface not of obstructive origin)
  - Loss of a part of the lung
  - Alveolar infiltrate (edema, pneumonia)
  - Atelectasis (hypoventilation, compression, insufficient amount of surfactant)

Spirometry



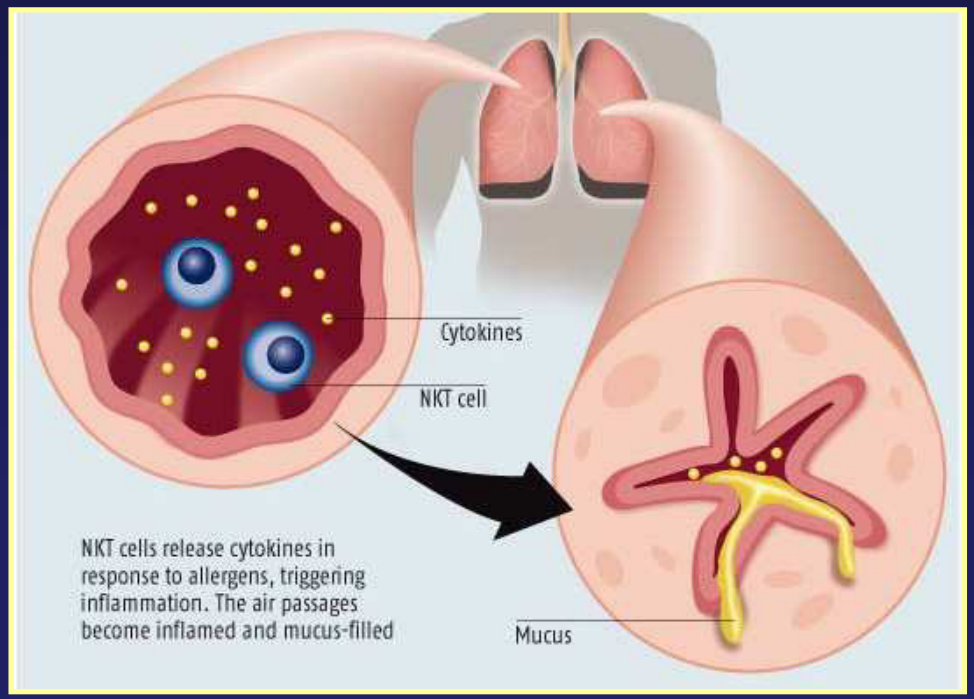
Tiffeneau index (FEV_1%):
(FEV_1/FVC)·100%

Etymology

- **Asthma** – a chronic condition characterized by recurrent bouts of dyspnea
  - **Cardiac asthma** – recurrent attacks of dyspnea due to failure of the left ventricle that can be accompanied by bronchoconstriction caused by pulmonary congestion
  - **Bronchial asthma** – recurrent bouts of dyspnea due to reversible obstruction of the lower airways
- **COPD** – **C**hronic **O**bstructive **P**ulmonary **D**isease

Histology of BA

- Impairment of the mucosal epithelium (this is only a functional damage initially, then progression may lead to partial epithelial abruption)
- Remodeling of the wall of bronchi and bronchioli:
  - smooth muscle hypertrophy and hyperplasia
  - thickening of the mucosa caused by secretory gland hyperplasia, lymphocyte and eosinophil cell infiltration, and inflammatory edema
- Increased mucus production (hypersecretion) leading to mucous plugs (inspissation)



Epidemiology of BA

- In developed countries, 2-12% of the population is affected by bronchial asthma (accurate assessment is hindered by varying definitions of asthma and methods of data collection)
- Worsening trend
- Early onset is typical (in childhood), but it can start in every age

Characteristics of BA

- Fluctuating course (acute attacks separated by intervals with no or mild symptoms)
- Attacks manifest in widespread narrowing of the lower airways (bronchi and, more importantly, bronchioli)
- In early stage of asthma, airway narrowing is totally reversible (later it tends to be partially reversible)
- Increased sensitivity towards stimuli causing bronchial and bronchiolar inflammation and/or constriction
- Enhanced secretory activity of glands and goblet cells in bronchial and bronchiolar mucosa
- Thickening of the wall of bronchi and bronchioli (especially in poorly controlled asthma)
- Good response to adequate treatment

Symptoms of an acute asthmatic attack (asthma exacerbation)

- Wheezing (specifically: sibilant rhonchus) during exhalation (mild or moderate bout) or during both inhalation and exhalation (severe bout)
- Shortness of breath, typically in response to specific (allergens, drugs) or non-specific provoking factors (exercise, previous viral respiratory infection, increase in vagal tone at night)
- Prolonged expiration
- Unproductive (dry) cough (especially at night)
- Tachycardia
- Pallor
- Cyanosis (in severe asthma, if the patient isn't anemic)

Major types of BA

- **Extrinsic asthma** (specific provoking factor can be identified, onset in childhood)
  - Allergen (mainly inhaled, occasionally food)
  - Drug (aspirin or another NSAID, β-blocker, opioid)
- **Intrinsic asthma** (specific provoking factor cannot be identified, onset in young adulthood)
- **Mixed asthma** (the identified specific provoking factors are only responsible for a part of attacks)

In all types (especially in vulnerable periods for the patient), an asthmatic attack can be induced by non-specific provoking factors, such as cold and/or dry air, irritant gases, previous viral infections in the lower airways, hyperventilation, psychosocial stress, and conditions increasing the vagal tone (e.g. sleeping)

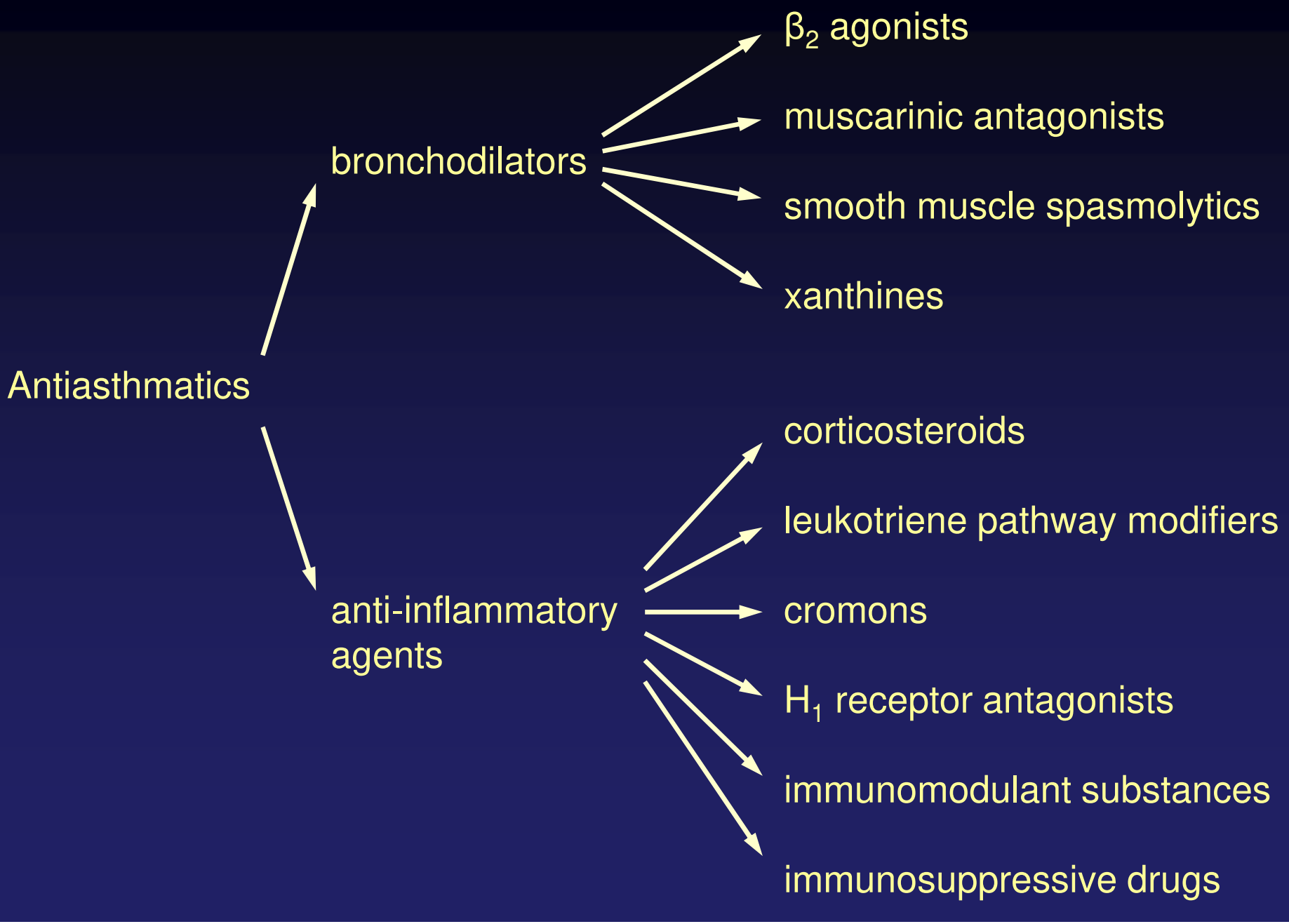
Possible pathogenic factors (and etiological theories) for BA

- **Immunological** – type I hypersensitivity (chiefly for extrinsic asthma)
- **Psychological** – psychosomatic disorder (mainly for intrinsic asthma)
- **Neurohormonal** – increased vagal and/or decreased sympathetic activity (and, in this latter one, increased α-adrenergic function relative to β-adrenergic activity)
- **Epithelial** – insufficient barrier function of airway epithelium

Therapy of BA

- **Causal treatment**
  - Elimination of the specific provoking factor (in extrinsic asthma)
  - Desensitization (in extrinsic asthma, if the number of allergens is low)
- **Symptomatic treatment**
  - Short-term relievers (direct bronchodilators)
  - Long-term controllers (anti-inflammatory agents)

Symptomatic treatment of asthma



Favorable and adverse effects of antiasthmatics I.

- **β_2 agonists**
  - Smooth muscle relaxation (by increasing the cAMP level in smooth muscle cells)
  - Reduction of mucus hypersecretion in airways
  - Inhibition of mastocyte degranulation
  - Enhancement of ciliary activity of bronchial and bronchiolar epithelium
  - Enhancement of anti-inflammatory effects of corticosteroids
  - Tachycardia (even in case of selective agents because of systemic vasodilation)
  - Skeletal muscle tremor
  - Hypokalemia (due to an increased potassium intake in skeletal muscle)
  - β_2 receptor downregulation and desensitization (in case of frequently used long-acting β_2 agonists applied without co-administration of corticosteroids, particularly for their effects exerted on tissues other than smooth muscle)

Favorable and adverse effects of antiasthmatics II.

- **Muscarinic antagonists**
  - Smooth muscle relaxation (by preventing the effect of acetylcholine released from the vagal nerve)
  - Reduction of mucus production (also an anti-acetylcholine action)
  - Some therapeutical benefit over β_2 agonists in patients with COPD or asthma-COPD overlap syndrome
  - Weak effect as compared to β_2 agonists (especially in extrinsic asthma)
- **Smooth muscle spasmolytics**
  - Smooth muscle relaxation (*via* inhibiting the phosphodiesterase /PDE/ and/or the L-type Ca^{2+} channels)
  - Some agents (roflumilast, cilomilast) show specificity towards PDE4, the major PDE type of airways
  - Weak effect as compared to β_2 agonists
  - Poor selectivity to the airways (in case of *per os* administration)

Favorable and adverse effects of antiasthmatics III.

- **Xanthines** (especially theophylline)
  - Smooth muscle relaxation (and enhancement of similar action of β_2 agonists, by increasing the cAMP level *via* phosphodiesterase inhibition and A_1 adenosine receptor blockade)
  - Inhibition of mastocyte degranulation (*via* phosphodiesterase inhibition and A_1 adenosine receptor blockade)
  - Increase in skeletal muscle contractility (*via* sensitizing the ryanodine receptor) that makes the work of respiratory muscles more effective
  - Increase in activity of histone deacetylase (and enhancement of the similar effect corticosteroids exert on histone deacetylase, leading to the repression of pro-inflammatory genes)
  - Narrow therapeutic window (need for plasma level monitoring)
  - Headache, insomnia, anxiety, skeletal muscle tremor, seizure
  - Anorexia, nausea, vomiting, abdominal discomfort
  - Tachycardia, arrhythmia

Favorable and adverse effects of antiasthmatics IV.

- **Corticosteroids**
  - Strong inhibition of practically every step of the inflammatory cascade leading to a decrease in mucosal edema and mucus hypersecretion
  - Strong immunosuppressive action contributing to the anti-inflammatory effect (with adverse effects milder than that of the so-called immunosuppressive drugs)
  - Increase in activity of histone deacetylase (and thereby repression of pro-inflammatory genes)
  - Increase in sensitivity to β_2 agonists
  - Slow development of the desirable effects
  - A small inhibitory effect on growth (for children)
  - Upon systemic administration, the common adverse effect of corticosteroids, such as: osteoporosis, hyperglycemia, irritability, hypertension, peptic erosion and ulcer, increased susceptibility to infections, suppression of adrenal cortex

Favorable and adverse effects of antiasthmatics V.

- **Leukotriene pathway modifiers**
  - Inhibition of leukotriene-mediated steps of the inflammatory cascade that leads to decreased mucosal edema as well as mucus production (an effect weaker than that of corticosteroids)
  - Inhibition of bronchial and bronchiolar reactivity to constrictor agents (great effectiveness against aspirin-induced asthmatic attack)
  - A weak bronchodilatory effect
  - Increase in activity of histone deacetylase (and thereby repression of pro-inflammatory genes)
  - Some patients do not respond to leukotriene pathway modifiers
  - Liver toxicity (in the case of zileuton)
  - Headache
  - Dyspepsia, diarrhea

Favorable and adverse effects of antiasthmatics VI.

- **Cromons**
  - A weak anti-inflammatory effect caused by mast cell stabilization and inhibition of some cell types involved in the inflammation, especially in extrinsic asthma
  - Safety (lack of toxicity)
  - Slow development of the desirable effects
  - Local irritation, mouth dryness
  - Nausea, anorexia, dysgeusia
- **H_1 receptor antagonists**
  - A weak anti-inflammatory effect shown in extrinsic asthma
  - Sedation
  - Except for their use as an adjunctive drug in seasonal asthma, H_1 receptor blockers are not able to significantly contribute to either the symptomatic relief or the control of bronchial asthma

Favorable and adverse effects of antiasthmatics VII.

- **Immunomodulant agents (biological therapy)**
  - Circumscript (not general) anti-inflammatory effects in extrinsic asthma
  - Irritation at the place of administration (in the skin)
  - High cost of the treatment
- **Immunosuppressive drugs**
  - Robust immunosuppressive and thereby strong anti-inflammatory effect (stronger than that of corticosteroids), mechanism of which depends on the particular agent (e.g. methotrexate is a folate antimetabolite type cytotoxic drug that additionally inhibits chemotaxis even in small doses)
  - Common adverse effects of immunosuppressive drugs, such as nausea, vomiting, mucosal ulceration, hepatotoxicity, anemia, increased susceptibility to infections, retardation in growth and development (for children)

Bronchodilators I.

- **β_2 agonists** (inhaled; in a severe bout: *per os* too)
  - Short-acting drugs (**SABA**): salbutamol (a.k.a. albuterol; Serevent), levosalbutamol (a.k.a. levalbuterol; Xopenex), terbutaline (Bricanyl – *iv.* too), fenoterol (Berotec, Berodual) - quick-relievers
  - Long-acting drugs (**LABA**): salmeterol (Serevent), formoterol (Atimos), clenbuterol (Spiropent), bambuterol (prodrug of terbutaline; Bambec), procaterol
  - Ultra long-acting (i.e. once-daily) drugs (**ultra-LABA**) – alone only in COPD; combined with inhaled corticosteroids (ICS) in BA: olodaterol (Striverdi Respimat), vilanterol (only in combination), abediterol (under investigation), indacaterol (Onbrez Breezhaler)

Bronchodilators II.

- **Muscarinic antagonists** (inhaled)
  - Short-acting drug: ipratropium bromide (Atrovent, Berodual) - quick-reliever
  - Long-acting drugs: tiotropium bromide (Spiriva), aclidinium bromide (Bretaris Genuair), glycopyrronium bromide (Seebri Breezhaler – only in COPD), umeclidinium bromide (Incruse – only in COPD)

Bronchodilators III.

- **Smooth muscle spasmolytics** (mainly *per os*)
  - Non-specific PDE inhibitor (with L-type Ca-channel inhibitory action): papaverine (Pavabid) (low priority)
  - Specific PDE4 inhibitors (only in COPD): roflumilast (Daxas, Daliresp), cilomilast (Ariflo)
- **Xanthines** (*per os*; in a severe attack: *iv.* too)
  - methylxanthines: theophylline (Retafyllin, Euphylong), aminophylline (complex of theophylline with ethylenediamine; Diaphyllin), caffeine (low priority)
  - propylxanthine: enprofylline (Nilyph)

Anti-inflammatory drugs I.

- **Corticosteroids** (inhaled; in a severe bout: *per os* and *iv.* too)
  - Only for inhalation (ICS): budesonide (Aerox, Miflonide), fluticasone (Flixotide), beclometasone (Clenil), flunisolide (AeroBid), ciclesonide (Alvesco)
  - Only *per os* or *iv.*: prednisolone (Di-Adreson), methylprednisolone (Medrol)
- **Leukotriene pathway modifiers** (*per os*)
  - $CysLT_1$ receptor antagonists (LTRA): zafirlukast (Accolate), montelukast (Singulair), pranlukast (Pranlukast)
  - 5-lipoxygenase inhibitor: zileuton (Zyflo)

Anti-inflammatory drugs II.

- **Cromons** (inhaled)
  - cromolyn (Intal), nedocromil (Tilade) (low-priority drugs)
- **H_1 receptor antagonists** (*per os*)
  - cetirizine (Zyrtec), levocetirizine (Xyzal), fexofenadine (Altiva) (low-priority drugs)

Anti-inflammatory drugs III.

- **Immunomodulant substances** (*sc.*) – efficacious but expensive biological therapy drugs to treat extrinsic asthma
  - omalizumab (humanized IgG specific to human IgE; Xolair)
  - quilizumab (humanized IgG specific to human IgE; under investigation)
  - benralizumab (blocking antibody specific to IL-5 receptor that decreases the eosinophilic granulocyte ADCT; Fasenra)
  - mepolizumab (humanized IgG specific to IL-5 that decreases the eosinophilic granulocyte ADCT; Nucala)
  - reslizumab (humanized IgG specific to IL-5 thereby decreasing the eosinophilic granulocyte ADCT; Cinqaero)

Anti-inflammatory drugs IV.

- lebrikizumab, tralokinumab (antibodies specific to IL-13; under investigation for extrinsic asthma)
- secukinumab (antibody specific to IL-17; Cosentyx)
- brodalumab (blocking antibody specific to IL-17; Siliq, Kyntheum)
- dupilumab (blocking antibody specific to IL-4 receptor that also inhibits the IL-13 pathway; Dupixent - under investigation to treat BA)

- **Immunosuppressive drugs** (*per os*, *sc.*, *im.*, *iv.*)
  - methotrexate (Metoject), ciclosporin (Sandimmun)
    „last resort" drugs

Thanks for your attention!