Pathologies and drugs of the respiratory apparatus
Prevalence of Asthma

Figure 1: Prevalence of asthma symptoms among 13-14 year olds (ISAAC).

Physiology of the respiratory apparatus

- The parasympathetic nerves mediate bronchial constriction and mucus secretion through an action on muscarinic M3-receptors.
- Sympathetic nerves innervate blood vessels (causing constriction) and glands (inhibiting secretion), but not airway smooth muscle.
- Circulating adrenaline acts on $\beta_2$-adrenoceptors to relax airway smooth muscle.
- The main neurotransmitter causing relaxation of airway smooth muscle is the NANC (non-adrenergic, non-cholinergic) inhibitory transmitter, thought to be nitric oxide.
- NANC excitatory transmitters are peptides released from sensory neurons.
Bronchial Asthma

Bronchial asthma

- Asthma is defined as recurrent reversible airway obstruction of airflow through the airway. The asthmatic attack comprises wheezing, cough and difficulty in breathing out; the airways resistance is increased—manifest as a decrease in the ‘forced expiratory volume in 1 second’ (FEV₁). Severe attacks are life threatening.
- Two characteristic features are:
  — underlying inflammatory changes in the airways
  — underlying bronchial hyper-responsiveness, i.e. abnormal sensitivity to stimuli.
- The development of allergic asthma involves exposure of genetically sensitive individuals to allergens; these cause activation of Th2 lymphocytes, which in turn generate cytokines that promote:
  — differentiation and activation of eosinophils
  — IgE production and release
  — expression of IgE receptors on mast cells and eosinophils.

- In many subjects, the asthmatic attack consists of two phases:
  — an immediate phase on exposure to eliciting agent, consisting mainly of bronchospasm
  — a later phase consisting of a special type of inflammation in the bronchioles comprising: vasodilatation, oedema, mucus secretion and bronchospasm caused by inflammatory mediators released from eosinophils and other cells. Activated, cytokine-releasing Th2 cells have an important role.
- Important mediators include leukotrienes C₄ and D₄, various chemotaxins and chemokines (in both phases) and tissue-damaging eosinophil proteins (delayed phase).
Forced expiratory volume (FEV1)

- FEV1 greater than 80% of predicted = normal
- FEV1 60% to 79% of predicted = mild obstruction
- FEV1 40% to 59% of predicted = moderate obstruction
- FEV1 less than 40% of predicted = severe obstruction
Bronchi of a normal and an asthmatic individual

**A** Normale

I muscoli dei bronchi sono rilassati, favorendo l'agevole passaggio del flusso d'aria.

**B** Asma

I muscoli dei bronchi sono stretti e ispessiti. I bronchi sono infiammati e pieni di muco e ciò ostacola il flusso d'aria.
Changes in the bronchioles in chronic asthma

- Submucosa
- Mucosa
- Infiltration of inflammatory cells, (mononuclear cells, eosinophils, etc.)
- Hypertrophied smooth muscle
- Dilated blood vessels
- Eosinophil
- Epithelium
- Thickened basement membrane
- Mucus plug with eosinophils and desquamated epithelial cells
- Mononuclear cell
- Mast cell
- Oedema
Asthma mechanisms

- Inflammation
- T lymphocytes
- Leukotrienes

Drugs

- Bronchodilators
- Anti-secretory
- Anti-leukotrienes
- Anti-inflammatory
Respiratory system drugs
Stages of asthma and pharmacological treatment

**Immediate phase**
- Eliciting agent: allergen or non-specific stimulus
- Mast cells, mononuclear cells
- Spasmogens: cysLTs, H, PGD₂
- Chemotaxins, Chemokines

**Late phase**
- Infiltration of cytokine-releasing Th2 cells, and monocytes, and activation of inflammatory cells, particularly eosinophils
- Mediators e.g. cysLTs, neuropeptides?, NO?, adenosine?
- EMBP, ECP
- Epithelial damage

- Bronchospasm, wheezing, coughing
- Inhibited by glucocorticoids

EMBP = eosinophil major basic protein
ECP = eosinophil cationic protein
Asthma Drugs

Drugs

• Bronchodilators
• Anti-secretory
• Anti-leukotrienes
• Anti-inflammatory
Antiasthma drugs: bronchodilators

- **β₂-Adrenoceptor agonists** (e.g. **salbutamol**)
  - are first-line drugs
  - They act as physiological antagonists of the spasmogenic mediators but have little or no effect on the bronchial hyper-reactivity.
  - Salbutamol is given by inhalation; its effects start immediately and last 3–5 hours, and it can also be given by intravenous infusion in status asthmaticus.
  - **Salmeterol** or **formoterol** are given regularly by inhalation; their duration of action is 8–12 hours.

- **Theophylline** (often formulated as **aminophylline**) is a third-line drug for asthma. Theophylline:
  - is a methylxanthine
  - inhibits phosphodiesterase and blocks adenosine receptors
  - has a **narrow therapeutic window**: unwanted effects include cardiac dysrhythmia, seizures and gastrointestinal disturbances
  - is given intravenously (by **slow** infusion) for status asthmaticus, or orally (as a sustained-release preparation) as add-on therapy to inhaled corticosteroids and long-acting β₂ agonists (step 4)
  - is metabolised in the liver by P450; liver dysfunction and viral infections increase its plasma concentration and half-life (normally approximately 12 hours)
  - interacts importantly with other drugs; some (e.g. some antibiotics) increase the half-life of theophylline, others (e.g. anticonvulsants) decrease it.

- **Cysteinyi leukotriene receptor antagonists** (e.g. **montelukast**) are third-line drugs for asthma. They:
  - competitively antagonise cysteinyi leukotrienes at CysLT₁ receptors
  - are used mainly as add-on therapy to inhaled corticosteroids and long-acting β₂ agonists (step 4).
Bronchodilator drugs

$\beta_2$-adrenergic
β₂-adrenergic receptors
Clinical use of $\beta_2$-adrenoceptor agonists as bronchodilators

- Short-acting drugs (salbutamol or terbutaline, usually by inhalation) to prevent or treat wheeze in patients with reversible obstructive airways disease.
- Salmeterol (long-acting bronchodilator) to prevent bronchospasm (e.g. at night or with exercise) in patients requiring long-term bronchodilator therapy.

$\beta_2$-adrenergic once-daily: indacaterol, carmoterol, milveterol, vilanterol, olodaterol

In combination with glucocorticoids
Side Effects

Desensitization

Tremor

Tachycardia

Arrhythmia
Bronchodilator drugs
Theophylline
Clinical use of theophylline

- As a second-line drug, in addition to steroids, in patients whose asthma does not respond adequately to β₂-adrenoceptor agonists.
- Intravenously in acute severe asthma.
- To reduce symptoms of chronic obstructive pulmonary disease.

Low therapeutic index (heart, intestine)
**Methylxanthines**

- Theophylline and its derivatives are most commonly used for the treatment of COPD and asthma.
- Caffeine, theophylline and theobromine are naturally occurring xanthine alkaloids which have qualitatively similar actions.

**Mechanism of action:**

- **Methylxanthines** inhibits cyclic nucleotide phosphodiesterase (PDEs), thereby preventing conversion of cAMP and cGMP to 5′-AMP and 5′-GMP, respectively. Inhibition of PDEs will lead to an accumulation of intracellular cAMP and cGMP. **Bronchodilataion**, cardiac stimulation and vasodilatation occur when cAMP level rises in the concerned cells. Theophylline and related methylxanthines are relatively nonselective in the **PDE subtypes inhibitor**.

- Theophylline is a competitive **antagonist at adenosine receptors**. Adenosine can cause bronchoconstriction in asthmatics and potentiate immunologically induced mediator release from human lung **mast cells**. Methylxanthines inhibits the adenosine action thereby casing bronchodilataion.
Theophylline

- Bronchodilatation
- Decrease pulmonary arterial pressure
- Increase the airway diameter

Central control of respiratory function

- Modulation of GABA<sub>a</sub> receptors
- Antagonism of adenosine receptors

- Mobilization of intracellular calcium
- Inhibition of phosphodiesterases (PDEs)

Methylxanthine
Asthma Drugs

Drugs

• Bronchodilators
• Anti-secretory
• Anti-leukotrienes
• Anti-inflammatory
Anti-secretory drugs

- Muscarinic receptor antagonists (e.g. ipratropium bromide) are second-line drugs
  - inhibits acetylcholine-mediated bronchospasm
  - binds to all muscarinic receptor subtypes ($M_1, M_2$ and $M_3$)
  - is given by aerosol inhalation.
Muscarnic Antagonists (M1-M3)

- Ipratropium
- Oxitropium
- Tiotropium bromide
Inhibit bronchoconstrictor effect of acetylcholine at M3 muscarinic receptors located on airway smooth muscle.

M2 muscarinic receptors on postganglionic nerve terminals act as feedback inhibitors.

Mucus gland: M3 (+)
Smooth muscle: M3 (+)
Asthma Drugs

Drugs

• Bronchodilators
• Anti-secretory
• Anti-leukotrienes
• Anti-inflammatory
Modifying agents of leukotrienes
Bronchial asthma drugs

Leucotrienes C4 and D4

- Cysteinyl-leukotriene receptor antagonists (e.g. montelukast):
  - competitively inhibit cysteinyl leukotriene receptors
  - inhibit exercise-induced bronchospasm and aspirin-induced asthma
  - have a bronchodilator action that is additive with $\beta_2$-adrenoceptor agonists
  - are of use mainly as add-on therapy for mild-to-moderate asthma
Action sites of leukotriene modifying drugs

Zileuton

Zafirlukast
Montelukast
Pranlukast

In combination with Beta2 agonists
Asthma Drugs

Drugs

• Bronchodilators
• Anti-secretory
• Anti-leukotrienes
• Anti-inflammatory
Anti-inflammatory drugs
Glucocorticoids
Role of T lymphocytes in asthma

APC = antigen presenting cell
P  = plasma cell
IgE = Immunoglobulins

- T cell
- Th0
- Th1
- Th2
- B
- P
- Eosinophils
- Mast cells
- IgE R
- IL-4
- IL-5
- IL-13
- Glucocorticoids
Clinical use of glucocorticoids in asthma

- Patients who require regular bronchodilators should be considered for glucocorticoid treatment (e.g. with inhaled beclometasone).
- More severely affected patients are treated with high-potency inhaled drugs (e.g. budesonide) and additional agents (e.g. slow release theophylline).
- Patients with acute exacerbations of asthma may require intravenous hydrocortisone and oral prednisolone.
- A ‘rescue course’ of oral prednisolone may be needed at any stage of severity if the clinical condition is deteriorating.
- Prolonged treatment with oral prednisolone, in addition to inhaled bronchodilators and steroids, is needed by a few severe asthmatics.
Glucocorticoids

- These reduce the inflammatory component in chronic asthma and are life-saving in status asthmaticus (acute severe asthma).
- They do not prevent the immediate response to allergen or other challenges.
- The mechanism of action involves decreased formation of cytokines, particularly those generated by Th2 lymphocytes, decreased activation of eosinophils and other inflammatory cells.
- They are given by inhalation (e.g. beclometasone); systemic unwanted effects are uncommon at moderate doses, but oral thrush and voice problems can occur. Systemic effects can occur with high doses but are less likely with mometasone because of its presystemic metabolism. In deteriorating asthma, an oral glucocorticoid (e.g. prednisolone) or intravenous hydrocortisone is also given.
Effects of glucocorticoids on gene expression

- GRE: glucocorticoid response element
- SLPI: Secretory leucoprotease Inhibitor
- MKP1: Mitogen-activated protein kinase phosphatase 1
- CBP: CREB binding protein
- IkB: inhibitor NF-κB
- GILZ: Gluc induced-leucine zipper

Trans-attivazione
- GRE effetti antinfiammatori
  - Annessina-1
  - SLPI
  - MKP-1
  - IkB-α
  - GILZ

Cis-repressione
- GRE negativi effetti collateralii
  - POMC
  - CRH
  - Osteocalcina
  - Cheratina

Trans-repressione
- NF-κB
- CBP

Espressione geni
- Citochine
- Chemochine
- Molecole di adesione
- Enzimi infiammatori
- Proteine infiammatorie
Mechanism of inhibition of expression of inflammatory genes (deacetylation) by glucocorticoids and theophylline

**Diagram**

Mechanism of inhibition of expression of inflammatory genes (deacetylation) by glucocorticoids and theophylline.

- **Stimoli infiammatori (es. IL-1β)**
  - IKK-2
  - NF-κB
  - p65
  - p50

- **Glucocorticoidi (basse dosi)**
  - GR
  - HDAC2 = histone deacetylase 2

- **Teofillina**

Geni infiammatori
- citochine
- chemochine
- molecole di adesione
- enzimi
- proteine

pCAF - activating factor; HAT - histone acetylation; HDAC2 = histone deacetylase 2
Pharmacokinetics of inhalatory glucocorticoids

- Deglutito il 90% (salvo che non si faccia uso del distanziatore o del risciacquo della bocca).
- Depositato nel polmone il 10%.
- Polmone
- Tratto Gastrointestinale
- Assorbimento dall'intestino
- Inattivazione di primo passaggio nel fegato.
- Fegato
- Effetti collaterali sistemici.
Effect of the spacer on the delivery of an inhalable aerosol

Grandi particelle di aerosol si depositano nella camera prima che il paziente le inali.

L’aerosol inalato viene arricchito da piccole particelle che raggiungono più rapidamente le basse vie aeree.
Classification of asthma severity and treatment
(Beta2 agonists)

<table>
<thead>
<tr>
<th>CLASSIFICAZIONE</th>
<th>EPISODI BRONCO-COSTRITTIVI</th>
<th>RISULTATI DEL FLUSSO DI PICCO O DELLA SPIROMETRIA</th>
<th>CONTROLLO A LUNGO TERMINE</th>
<th>SOLLIEVO RAPIDO DEI SINTOMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lieve intermittente</td>
<td>Meno di due per settimana</td>
<td>Quasi normale*</td>
<td>Nessuna terapia quotidiana</td>
<td>$\beta_2$-agonisti a breve durata $\star$</td>
</tr>
<tr>
<td>Lieve persistente</td>
<td>Più di due per settimana</td>
<td>Quasi normale*</td>
<td>Corticosteroidi inalatori a bassa dose</td>
<td>$\beta_2$-agonisti a breve durata $\star$</td>
</tr>
<tr>
<td>Moderata persistente</td>
<td>Quotidiani</td>
<td>Dal 60 all’80% del normale</td>
<td>Corticosteroidi inalatori a dose medio-bassa e un $\beta_2$-agonista a lunga durata §</td>
<td>$\beta_2$-agonisti a breve durata $\star$</td>
</tr>
<tr>
<td>Severa persistente</td>
<td>Continui</td>
<td>Meno del 60% del normale</td>
<td>Corticosteroidi inalatori ad alta dose e un $\beta_2$-agonista a lunga durata §</td>
<td>$\beta_2$-agonisti a breve durata $\star$</td>
</tr>
</tbody>
</table>

* Salbutamol, pirbuterol, terbutaline (15-30 min up to 4-6 h)
§ Salmeterol, formoterol (up to 12 h)
Prophylaxis
Cromoglycate and nedocromil
Hypersensitivity reactions mediated by immunoglobulins

- Inhibits macrophages, eosinophils, neutrophils, monocytes
- Reduces hyperpolarization in inflamed cells which activates increased Ca++ responsible for degranulation
Anti-IgE treatment
Hypersensitivity reactions mediated by immunoglobulins

**Omalizumab**

In severe allergic asthma
Mastocita o basofilo

FceRI

IgE

Murino

Umano

AB omalizumab binds IgE receptor
Therapeutic Strategies

- Long-Acting Beta-adrenergic Agonist (LABA) + glucocorticoid (GC) anti-inflammatory by inhalation

- LABA + GC via inhalation + slow-release theophylline or leukotriene inhibitors or tiotropium bromide

- Addition of oral treatment with GC
Chronic obstructive pulmonary disease (COPD)
## Treatment of stable chronic obstructive pulmonary disease (COPD)

<table>
<thead>
<tr>
<th>STADIO</th>
<th>CARATTERISTICHE</th>
<th>CONTROLLO A LUNGO TERMINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: BPCO lieve</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; superiore all’80% del previsto</td>
<td>Broncodilatatori a breve durata d’azione al bisogno.</td>
</tr>
<tr>
<td>II: BPCO moderata</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; dal 50 all’80% del previsto</td>
<td>Trattamento costante con uno o più broncodilatatori. Glucocorticoidi inalatori.</td>
</tr>
<tr>
<td>III: BPCO severa</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; meno del 30% del previsto</td>
<td>Trattamento costante con uno o più broncodilatatori. Glucocorticoidi inalatori. Antibiotici per le esacerbazioni acute della BPCO caratterizzate da aumento del volume e della purulenza delle secrezioni. Ossigenoterapia a lungo termine.</td>
</tr>
</tbody>
</table>

FEV<sub>1</sub> = forced expiratory volume 1 sec
## Drugs for chronic asthma therapy: pharmacokinetic aspects

<table>
<thead>
<tr>
<th>Farmaci</th>
<th>Via di somministrazione</th>
<th>Biodisponibilità</th>
<th>Vd</th>
<th>Emivita</th>
<th>Legame alle proteine plasmatiche</th>
<th>Frequenza di somministrazione</th>
<th>Metabolismo</th>
<th>Eliminazione</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoidi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>beclometasone</td>
<td>inalatoria</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6 – 12 h</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>budesonide</td>
<td>inalatoria</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>12-24 h</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>flunisolide</td>
<td>inalatoria</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>12-24 h</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>fluticasone</td>
<td>inalatoria</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>12 h</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>triamcinolone</td>
<td>inalatoria</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6-12 h</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antagonisti dei leucotrieni</th>
<th>per os</th>
<th>58-66%</th>
<th>8 -11 L</th>
<th>2,7-5,5 h</th>
<th>&gt; 99%</th>
<th>ogni 24 h</th>
<th>epatico: CYP 3A4 e 2C9</th>
<th>prevalentemente biliare (farmaco e metaboliti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>montelukast</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>zafirlukast</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cromoni</td>
<td>inalatoria</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>ogni 6 h</td>
<td>epatico: demetilazione, ossidazione</td>
</tr>
<tr>
<td>Teofillina**</td>
<td>per os</td>
<td>90-100%</td>
<td>35 L</td>
<td>8 h***</td>
<td>60%****</td>
<td>ogni 12 h</td>
<td>renale</td>
<td></td>
</tr>
</tbody>
</table>
## Anti-asthmatic drugs: side effects and dosage

<table>
<thead>
<tr>
<th>Farmaco</th>
<th>Posologia</th>
<th>Effetti collaterali</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucocorticoidi inalatori</strong></td>
<td></td>
<td>locali: raucedine, candidosi oro-faringea; sistemici: riduzione cortisolemia*, osteoporosi, cataratta (rara), atrofia cutanea**, porpora**, possibile ritardo dell'accrescimento</td>
</tr>
<tr>
<td>beclometasone</td>
<td>100 – 2000 µg</td>
<td></td>
</tr>
<tr>
<td>budesonide</td>
<td>100 – 1600 µg</td>
<td></td>
</tr>
<tr>
<td>flunisolide</td>
<td>500 - &gt; 2000 µg</td>
<td></td>
</tr>
<tr>
<td>fluticasone</td>
<td>100 – 2000 µg</td>
<td></td>
</tr>
<tr>
<td>triamcinolone</td>
<td>400- &gt; 2000 µg</td>
<td></td>
</tr>
<tr>
<td><strong>β&lt;sub&gt;2&lt;/sub&gt;-Adrenergici a lunga durata di azione</strong></td>
<td></td>
<td>tremore, possibile aumento della iperreattività bronchiale se non associati a glucocorticoidi inalatori; iperglicemia, ipopotassiemia, aumento delle concentrazioni plasmatiche di acido lattico. A dosi superiori a quelle terapeutiche: tachicardia, palpitazioni.</td>
</tr>
<tr>
<td>formoterolo</td>
<td>9-24 µg</td>
<td></td>
</tr>
<tr>
<td>salmeterolo</td>
<td>50-100 µg</td>
<td></td>
</tr>
<tr>
<td><strong>Antagonisti dei leucotrieni</strong></td>
<td></td>
<td>cefalea, dispepsia, dolore addominale; associazione con sindrome di Churg-Strauss</td>
</tr>
<tr>
<td>montelukast</td>
<td>10 mg (nell’adulto); 5 mg (nel bambino età 6-14 anni)</td>
<td></td>
</tr>
<tr>
<td>zafirlukast</td>
<td>40 mg</td>
<td>cefalea, dispepsia, dolore addominale, aumento delle concentrazioni plasmatiche di transaminasi; associazione con sindrome di Churg-Strauss</td>
</tr>
<tr>
<td><strong>Cromoni</strong></td>
<td></td>
<td>molto raramente broncostrizione, edema laringeo, artralgie, angioedema, cefalea, eruzioni, cutaneae</td>
</tr>
<tr>
<td>nedocromil sodico</td>
<td>8 mg</td>
<td>anoressia, nausea, emesi, insonnia, agitazione, palpitazioni, ipotensione; ad alte concentrazioni plasmatiche***, aritmie e convulsioni</td>
</tr>
<tr>
<td>Teofillina</td>
<td>0,4-0,5 mg/kg/h</td>
<td></td>
</tr>
</tbody>
</table>