Demonstration of the effect of bronchodilators in an experimental model of bronchial asthma:

- **Introduction:** Asthma is a syndrome characterized by airflow obstruction that varies markedly, both spontaneously and with treatment. Asthmatics harbor a type of inflammation in the airways that makes them more responsive than non-asthmatics to a wide range of triggers, leading to excessive narrowing with consequent reduced airflow and symptomatic wheezing, dyspnea and cough. Narrowing of the airways is usually reversible, but in some patients with chronic asthma there may be an element of irreversible airflow obstruction.

- **Drugs for asthma can be broadly divided into two main classes:**
  - Bronchodilators.
  - Anti-inflammatory.

- **Objective:** To demonstrate the effect of salbutamol on histamine-induced bronchoconstriction in an experimental animal.

- **Parameter measured:** Respiratory overflow – ROF (indirect measure of airway resistance).

- **Animal used:** Anesthetized Guinea pig.

- **Drugs and chemicals used:**
  - Salbutamol 100 mcg aerosol.
  - Histamine 1% aerosol.
  - Urethane 25% (anesthetic drug).

- **Procedure:** A guinea pig is anesthetized with urethane 25% administered intraperitoneally in a dose of 1.5 g/kg body weight. Once anesthetized, the trachea of the animal is exposed through an incision in the neck region. Through a cut in the trachea, a tracheal cannula is inserted. This cannula is connected by tubes to a respiratory pump and a bronchospasm measuring unit (airflow sensor). The respiratory pump ventilates the animal (tidal volume and respiratory rate being adjustable). Histamine is administered as an aerosol to produce bronchoconstriction, increasing airway resistance and respiratory overflow (ROF). This is followed by administration of salbutamol and its effect is observed.

- **Results:** Salbutamol reverses histamine-induced bronchospasm.

- **Inhalation of drug by metered-dose inhalers in asthma:**

  - **Advantages:**
    - Delivers the drug directly to the site of action.
    - Allows rapid relief of bronchoconstriction with short-acting $\beta_2$-agonists (bronchodilators).
    - Causes less systemic adverse effects as a result of using small dosage of drugs.

  - **Disadvantages:**
    - It is difficult to use for children even with supervision (this problem can be overcome by using a spacer device).
- **Recommendations for management of asthma:**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Symptoms</th>
<th>Recommended treatment (acute)</th>
<th>Recommended treatment (long-term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild intermittent</td>
<td>Symptoms &lt; 2 a week; nighttime symptoms &lt; 2 a month</td>
<td>Short-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist</td>
<td>No daily medication required</td>
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<tr>
<td>Mild persistent</td>
<td>Symptoms &gt; 2 a week; nighttime symptoms &gt; 2 a month</td>
<td>Short-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist</td>
<td>Daily inhaled corticosteroid, cromolyn or nedocromil</td>
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<tr>
<td>Moderate persistent</td>
<td>Symptoms daily; nighttime symptoms &gt; 1 a week</td>
<td>Short-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist</td>
<td>Inhaled corticosteroid (medium dose) and long-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>Continual symptoms; frequent</td>
<td>Short-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist</td>
<td>Inhaled corticosteroid (high dose), long-acting β&lt;sub&gt;2&lt;/sub&gt;-agonist and oral corticosteroids</td>
</tr>
</tbody>
</table>

**Bronchodilators**

- β<sub>2</sub>-agonists (increase cAMP)
  - Albuterol (short-acting), salmeterol (long-acting) and indacaterol (COPD)
  - Adverse effects: tremors, tachycardia and anxiety

- Methylxanthines (increase cAMP and block adenosine)
  - Aminophylline, theophylline (metabolized by the liver) and roflumilast (COPD)
  - Adverse effects: CVS, alertness, nausea and vomiting

- Antimuscarinic drugs (used in COPD)
  - Ipratropium and tiotropium
Anti-inflammatory (management)

Corticosteroids
- Fluticasone (inhalation), beclomethasone (inhalation), budesonide (inhalation) and prednisone (oral)
  - Inhibiting IgE production, enhancing β2 adrenoreceptors, inhibiting synthesis of PG & LT, reducing formation of cytokines and eosinophils
  - Adverse effects: oropharyngeal candidiasis and hoarsness

Leukotriene inhibitors
- Lipoxigenase inhibitors: zileuton
- Receptor antagonist: montelukast and zafirlukast

Anti-IgE antibodies
- Omalizumab

Mast cell stabilizers
- Cromolyn sodium and nedocromil