WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

ASTHMA: CAUSES, SYMPTOMS, AND TREATMENT

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ABSTRACT:

Asthma is a common chronic disease characterized by episodic or persistent respiratory symptoms and airflow limitation. Asthma treatment is based on a stepwise and controlbased approach that involves an iterative cycle of assessment, adjustment of the treatment and review of the response aimed to minimize symptom burden and risk of exacerbations. Anti-inflammatory treatment is the mainstay of asthma management. In this review we will discuss the rationale and barriers to the treatment of asthma that may result in poor outcomes. The benefits of currently available treatments and the possible strategies to overcome the barriers that limit the achievement of asthma control in reallife conditions and how these led to the GINA 2019 guidelines for asthma treatment and prevention will also be discussed.

Keywords: Asthma, Anti-inflammatory treatment, Disease control, Patient outcomes.

Introduction

Asthma is defined as a condition marked by significant short-term variations in resistance to airflow within the intrapulmonary airways. Professor Scadding noted that this definition may be expanded by mentioning known causes and clarified that “wide variations” refers to changes that are clinically important in symptoms and response to treatment.
Defining asthma is challenging, especially in adults, because chronic airflow obstruction can result from asthma, chronic bronchitis, emphysema, or combinations of these. Many patients show fluctuations in airflow without returning to normal lung function, and smoking, pollution, or occupational exposures can add irreversible components that blur distinctions between diseases.
Using Scadding’s general framework, childhood asthma can be defined as recurrent episodes of cough or wheeze with symptom-free intervals, caused by reversible airflow obstruction that improves significantly with bronchodilators or steroids. This definition must be applied with clinical judgement. It includes most children with recurrent post-bronchiolitic wheeze but excludes isolated first-time bronchiolitis

TYPES OF ASTHMA: INHALED ASTHMA

Introduction

Inhaled therapy is now central to asthma management, especially inhaled corticosteroids (ICS). Its development reflects major medical advancements in the late 20th century. The first major step was the introduction of the pressurised metered-dose inhaler (pMDI) in 1956, which paved the way for modern inhaled treatments.

Inhaled Corticosteroid Therapy (ICS)

Glucocorticosteroids are the most effective drugs for asthma. Cortisone was first extracted in 1936, and its benefits in asthma were confirmed by 1956. Soon after, prednisolone and hydrocortisone were developed. However, long-term systemic steroid use caused serious side effects such as hypertension, osteoporosis, diabetes, obesity, skin thinning, and bruising.
To reduce these risks, inhaled steroids were created. Beclomethasone dipropionate (BDP), introduced in the early 1970s, became the first widely used inhaled corticosteroid. Early studies—both uncontrolled and controlled—showed its remarkable effectiveness, transforming asthma care. Initially, many general practitioners were hesitant due to concerns arising from systemic steroid side effects, so inhaled steroids were mainly initiated by hospital specialists.

Severe Asthma

A clear definition of severe asthma is essential because asthma represents multiple phenotypes rather than a single disease. Various national and international groups have proposed definitions based on symptoms, lung function, exacerbations, and the need for high-dose corticosteroids.
The original European Network definition classified severe asthma as asthma that remained difficult to control despite a year of specialist assessment and treatment. A more detailed definition was proposed by the American Thoracic Society (ATS) in 2000, requiring **one major criterion** (continuous high-dose oral or inhaled steroids for at least half of the previous year) plus **two of seven minor criteria**, which considered lung function, disease stability, exacerbation frequency, and additional controller medications. These criteria applied only after confirming good adherence and management of contributing factors.

Treatment of Severe Asthma

Managing severe asthma remains challenging. Corticosteroids—especially high-dose inhaled forms—are still the main treatment because of their broad anti-inflammatory effects. Patients who have not previously used potent inhaled corticosteroids (ICS) should undergo a trial, although it is unclear whether smaller-particle ICS improve distal airway inflammation. Some patients respond poorly to steroids and may require high-dose systemic therapy. Leukotriene modifiers can help, particularly in aspirin-sensitive patients (20–25% of severe cases). 5-lipoxygenase inhibitors may also be beneficial. Long-acting β-agonists, effective for milder asthma, are often less helpful in severe disease. Immunosuppressants like methotrexate or cyclosporine offer limited benefit and cyclosporine carries significant risks. Anti-IgE therapy reduces hospitalisations in moderate–severe allergic asthma, though its role in very severe or non-allergic asthma is uncertain. Targeting eosinophilic inflammation may be valuable, since persistent eosinophilia predicts good steroid responsiveness. Therapies such as imatinib or mepolizumab (anti-IL-5) are being studied, along with other biologic approaches targeting TNF, Th2 cytokines, or chemokine pathways.

Defining Asthma

Diagnosing asthma—especially in preschool children—is often difficult. The International Paediatric Asthma Consensus Group defines asthma as episodic wheeze or cough in a setting where asthma is likely and other conditions have been excluded. However, this definition is problematic for cystic fibrosis (CF) patients. The ERCF definition—based on broad "asthma-like symptoms" such as hyperreactivity or prolonged exhalation—is too nonspecific to reliably diagnose asthma in CF patients.

Diagnosing Asthma

In non–cystic fibrosis (CF) patients, asthma diagnosis often relies on history and clinical clues, but many of these are less helpful in CF. Wheezing timing (e.g., during exercise or at night) is nonspecific, and coughing is common in all CF patients. The strongest predictors of asthma risk are a personal or family history of atopy (eczema, allergic rhinitis, or asthma). Physical examination is not very useful since many CF patients show signs like hyperinflation. Some investigations may offer additional clues.

Environmental Exposures and Asthma

Indoor Pollution

Indoor pollutants play a larger role in asthma severity than outdoor pollution.

- Environmental Tobacco Smoke (ETS) is the strongest indoor predictor of asthma morbidity. Children exposed to ETS have higher symptom frequency, worse lung function, and up to 2.5× greater asthma risk.

Nitrogen Dioxide (NO_2)

Gas stoves and heaters produce NO_2. NCICAS homes showed elevated levels, with 24% above 40 ppb—levels associated with increased risk of acute and chronic lung disease. Poor ventilation worsened exposure.

Indoor Allergens

Allergen sensitization is common: 60–80% of asthmatic children have at least one positive skin test.
In inner-city environments, the pattern differs:

- More sensitivity to molds and cockroaches
- Less to dust mites, cats, and dogs

Inflammation, Symptom Perception, and Asthma

Asthma symptoms such as cough and breathlessness arise from chronic airway inflammation and complex interactions between nerve stimulation, brain

processing, and psychological factors. Symptom perception varies widely between individuals.

- Others may *over-perceive* symptoms or misattribute unrelated sensations to asthma.
- In children, perception is highly variable; parents and children often under-recognize exacerbations. Studies show:

Role of Eosinophilic Inflammation

Eosinophils release neurotoxins that can impair sensory nerve pathways involved in perceiving bronchoconstriction. Studies show:

- Asthmatics with high eosinophilic inflammation often perceive less bradykinin-induced dyspnea.
- Severe asthma patients have reduced perception of bronchoconstriction after methacholine or hypertonic saline challenge, and this reduced perception is inversely related to sputum eosinophil levels.
- In mild asthma, the relationship may be positive, meaning more eosinophils are linked to stronger perception.

Role of Inflammatory Mediators

Activation of lung mast cells (e.g., by adenosine) releases mediators like histamine and prostaglandins that stimulate C-fiber nerves, contributing to dyspnea.
Key findings:

- Inhaled prostaglandin E_2 (PGE_2) heightens the sensation of dyspnea during exercise without changing airway mechanics, indicating a strong vagal sensory component.
- PGE_2 increases C-fiber sensitivity to irritants and mechanical stimuli.
- Dyspnea perception correlates with reduced bronchodilator response to deep inspiration, indicating underlying airway inflammation.

Role of Cytokines in Asthma Pathophysiology

Cytokines are central regulators of chronic airway inflammation in asthma. They are produced by inflammatory cells (eosinophils, mast cells, macrophages, lymphocytes) and structural cells (epithelial and endothelial cells). These cytokines:

- Drive type of inflammation and associated airway changes.
- Contribute to airway hyperresponsiveness (AHR) and epithelial damage.

Key cytokines include:

- IL-3 – supports mast cell survival
- IL-4 – promotes IgE production and VCAM-1 expression
- IL-5 – essential for eosinophil differentiation and survival
- IL-1, IL-6, GM-CSF, TNF-α – enhance AHR, disrupt epithelial barrier, amplify inflammation

Blockade of IgE

IgE is a key trigger of allergen-induced inflammation.
Omalizumab, an anti-IgE monoclonal antibody:

- Blocks IgE binding to high- and low-affinity receptors.
- Reduces mast cell activation and IgE-mediated allergen uptake.
- Improves symptoms in severe allergic asthma and reduces oral steroid use.
- Helps comorbid conditions like rhinitis, urticaria, sinusitis, and allergic bronchopulmonary aspergillosis.

Limitations:

- Only 1–2% of asthmatics are eligible.
- About one-third respond strongly, one-third moderately, one-third poorly.
- Long-term treatment may reduce endogenous IgE production; benefits persist up to 7 years.
- Economic concerns limit widespread use.

Newer anti-IgE strategies:

- High-affinity antibodies (e.g., RG7449)
- Anti-CD23 therapy
- Inhibitors targeting FcεRI receptors or IgE conformational changes

Anti-IL-5 Therapies

Mepolizumab, reslizumab, benralizumab

- Significantly reduce blood and sputum eosinophils.
- Early trials showed eosinophil reduction but no major clinical improvement in moderate–severe asthma.
- Possible reason: only partial removal of eosinophils from airway tissue (due to IL-5 receptor loss on ~50% of cells).

Emerging Anti-Mediator Therapies

Two major new classes already in clinical use:

1. **Leukotriene inhibitors** – for mild to moderate asthma.
2. **Anti-IgE therapy (omalizumab)** – for severe allergic asthma

These developments reflect a shift toward targeting specific mediators, though many mediators have limited roles in asthma.

Expanding Therapeutic Targets

New drug development now explores:

- Immune cells
- Cytokines & chemokines

Asthma is **heterogeneous**, with multiple phenotypes in adults and children, each showing different treatment responses.

The Challenge of Severe, Poorly Controlled Asthma

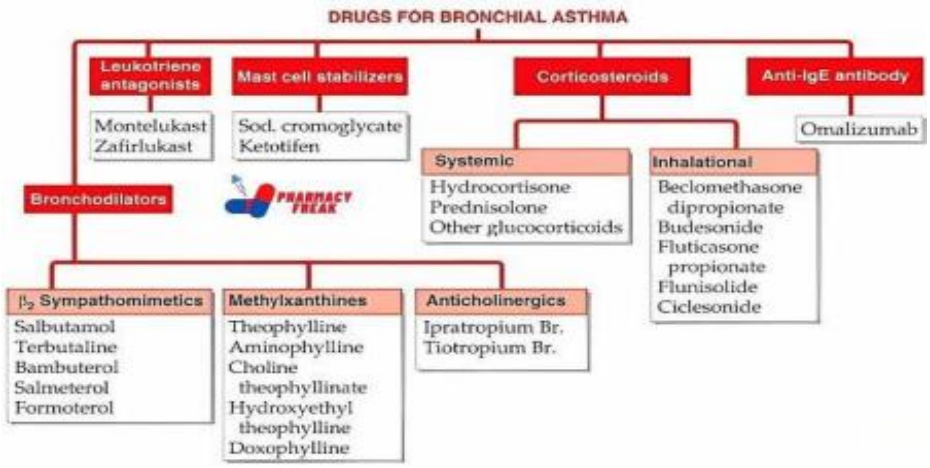
- These patients often show **corticosteroid insensitivity** (steroid-dependent or steroid-resistant).
- Severe asthma ≠ always steroid-resistant — the terms overlap but are not identical.

Research Efforts

- ENFUMOSA and SARP programs highlight the need to:
  - Understand **cellular and molecular mechanisms** of severe asthma,
  - Identify **new therapeutic targets**,

Drugs Used in Asthma

BASIC PHARMACOLOGY OF AGENTS USED IN THE TREATMENT OF ASTHMA



SYMPATHOMIMETIC AGENTS:

Adrenoceptor Agonists in Asthma

Adrenoceptor agonists are key drugs in asthma management because they relax airway smooth muscle, inhibit mast-cell mediator release, enhance mucociliary clearance, and reduce microvascular leakage. Their effects occur mainly through β-receptor stimulation, which increases intracellular cAMP and activates adenylyl cyclase. Although airway smooth muscle has no strong sympathetic innervation, it contains functional adrenoceptors, making β-agonists effective bronchodilators. Common adverse effects include tachycardia and muscle tremor due to β1 and β2 stimulation.

Administration

Inhalation is preferred because it delivers drug directly to airways with minimal systemic effects. However, only about **10–20%** of inhaled aerosol reaches the bronchi; most deposits in the mouth or pharynx. Slow, deep inhalation with a breath-hold improves deposition.

Non-Selective Agents

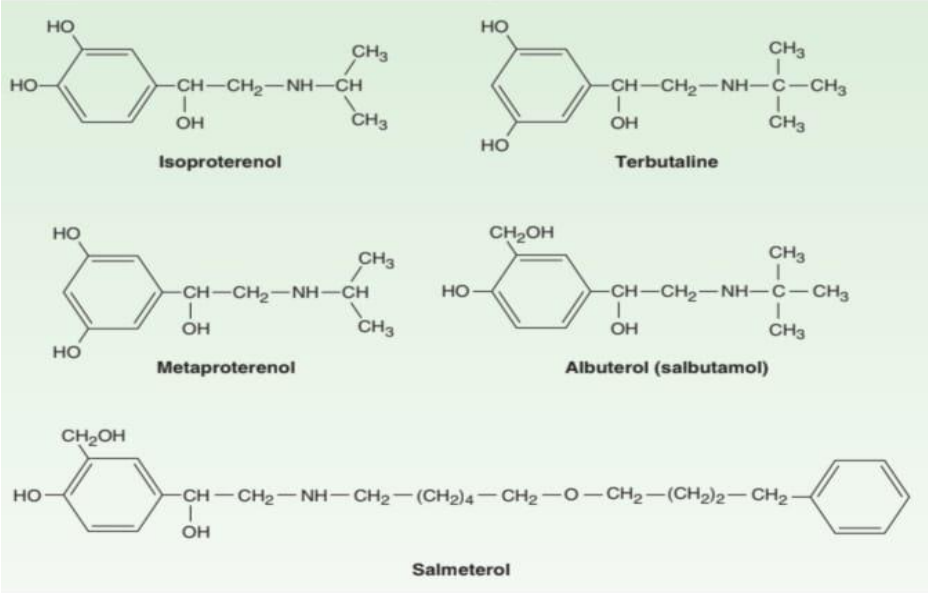
- Epinephrine: Potent, rapid bronchodilator (inhaled or subcutaneous). Peak effect in 15 min, lasts 60–90 min. Limited by side effects (tachycardia, arrhythmias) due to α and β1 action. Now replaced by selective β2 agonists except in anaphylaxis.
- Ephedrine: Oral, long-acting but weak and with CNS effects. Rarely used today.
- Isoproterenol: Strong bronchodilator but caused arrhythmias and was linked to asthma deaths in the 1960s. No longer widely used.

β2-Selective Agonists

Drugs like albuterol (salbutamol) are now the most commonly used agents for acute bronchoconstriction. They differ structurally from epinephrine and provide:

- Higher β2 selectivity
- Fewer cardiac side effects

MECHANISM OF ACTION:



β_2-Selective Bronchodilators & Inhalation Methods

MDIs (metered-dose inhalers) for pirbuterol, metaproterenol, terbutaline, and albuterol produce bronchodilation similar to isoproterenol.

- Onset: Peak effect in 15–30 minutes
- Duration: 3–4 hours
- All can also be given via handheld nebulizer, but nebulizers require much higher doses (2.5–5 mg vs. 100–400 mcg) without added benefit.
- Nebulizers are reserved for patients unable to coordinate MDI use.

Isomers

Most β_2-agonists contain R- and S-isomers; only the R-isomer is active.

- Levalbuterol (pure R-isomer) was developed because the S-isomer may promote inflammation, but its clinical advantage remains uncertain.

Oral and Injectable Forms

- Oral albuterol and terbutaline are available but rarely preferred due to more systemic side effects (tremor, anxiety, weakness).
- Starting with half-strength tablets can improve tolerance.
- Terbutaline can be given subcutaneously (0.25 mg) for severe asthma when inhaled therapy fails or is unavailable; repeated doses risk cumulative effects.

Long-Acting β_2-Agonists (LABAs)

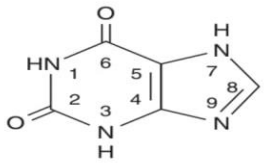
- Formoterol (full agonist) and salmeterol (partial agonist) act for ≥12 hours due to high lipid solubility that allows membrane retention or binding to nearby "mooring" sites.
- LABAs improve control when used with inhaled corticosteroids (ICS) but must not be used alone because they lack anti-inflammatory action.

Ultra-Long-Acting Agent

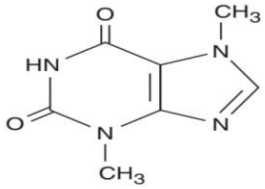
- Indacaterol, taken once daily, is approved only for COPD.

- No sufficient data support its use in asthma.

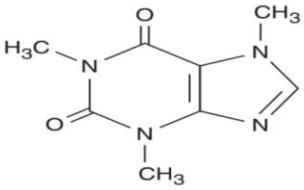
METHYLXANTHINE DRUGS:



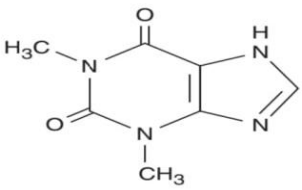
Xanthine



Theobromine



Caffeine



Theophylline

Asthma Pharmacotherapy & Management

Methylxanthines

Key agents: theophylline (most used), theobromine, caffeine.
Their role in asthma has declined due to better inhaled therapies, but theophylline remains valuable in low-resource settings due to its very low cost.

Mechanism of Action

- PDE inhibition (main hypothesis): increases intracellular cAMP, reducing inflammation and relaxing smooth muscle. PDE4 is most relevant for airway effects.
- Adenosine receptor blockade: may prevent bronchoconstriction and histamine release.
- Enhances histone deacetylation**:** improves corticosteroid responsiveness, especially in smokers and some COPD patients.

Pharmacodynamic Effects

- CNS: alertness at low doses; high doses → tremor, anxiety, seizures.
- Cardiovascular: ↑ HR and contractility; arrhythmias at high doses.
- GI: ↑ gastric acid and enzyme secretion.
- Renal: mild diuresis (not therapeutically useful).
- Smooth muscle: bronchodilation, inhibition of histamine release.
- Skeletal muscle: improves diaphragm function, reduces dyspnoea even in fixed airflow obstruction.

Antimuscarinic Agents

Derived from atropine (originally noted in *Datura stramonium* use in India).

Mechanism

- Block muscarinic receptors, preventing acetylcholine-mediated bronchoconstriction and mucus secretion.

- Useful mainly against vagal (parasympathetic) bronchospasm.
- Minimal effect on non-muscarinic stimuli at therapeutic doses.

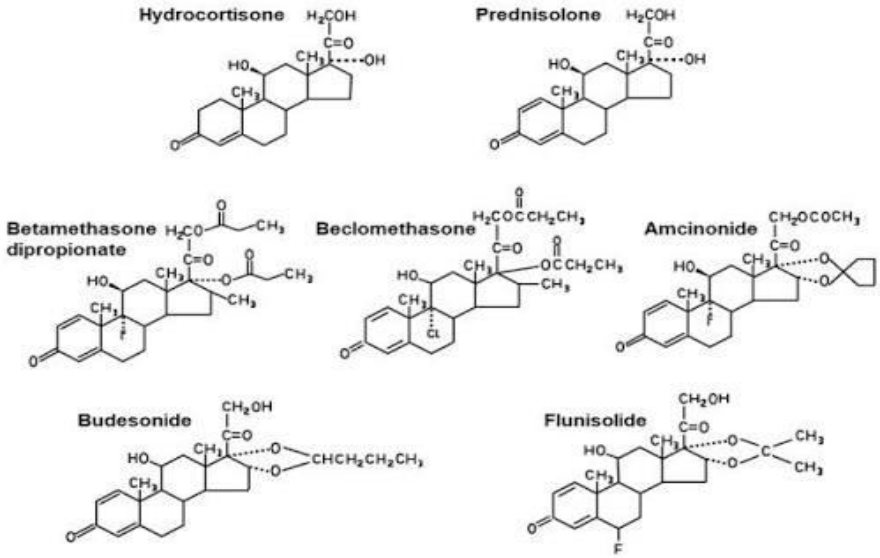
Modern agents (like ipratropium) are poorly absorbed systemically and have fewer atropine-like side effects.

Corticosteroids (ICS)

Most effective anti-inflammatory therapy for asthma but limited by poor adherence due to "steroid phobia."

Uses

- Reduce airway inflammation, bronchial hyperreactivity, and exacerbations.
- Improve the response to β_2-agonists.



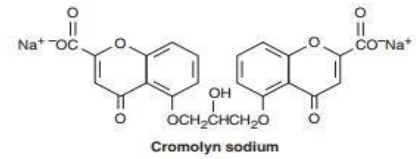
Anti-IgE Therapy

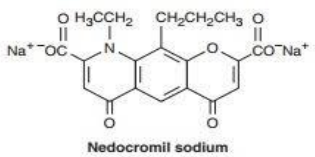
Omalizumab is used for:

- Severe, persistent asthma
- Poor control despite high-dose ICS + LABA

LEUKOTRIENE ANTAGONISTS:

CROMOLYN & NEDOCROMIL


Cromolyn sodium


Nedocromil sodium

Other Anti-inflammatory Therapies

For steroid-dependent chronic asthma:

- Early optimism for methotrexate/gold therapy not confirmed.
- Cyclosporine shows some benefit but high toxicity limits use.
- Etanercept (TNF-α blocker) shows experimental benefit.

Management of Acute Asthma

Treatment requires close monitoring and repeated lung function checks.

Mild attack

- **Inhaled β_2-agonist** (as effective as SC epinephrine).

Severe attack

- Oxygen
- Frequent/continuous nebulized albuterol
- Systemic corticosteroids (prednisone or methylprednisolone)
  If deteriorating → intubation and mechanical ventilation may be lifesaving.

Prospects for Prevention

Primary prevention strategies are needed due to rising global asthma rates.

- Strict allergen avoidance in infancy is NOT effective.
- Early-life exposure to pets or farm environments seems protective.

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