ASTHMA

Risk Factors

- Family history of asthma or other atopic diseases (eczema, hayfever)
- Having eczema or hayfever currently or as a child
- Living in an industrialised area → more exposure to airborne pollutants, less exposure to microbial antigens (hygiene hypothesis)
- Exposure to airborne pollutants → through occupation (coal mining) etc.
- Occupation → associated with 10-15% of adult asthma cases
- Exposure to stress (increased catecholamine production results in inflammation)
- Infection, particularly with viruses (induces smooth muscle contraction)

Genetic Factors

- HLA-DR/Q → the type of MHC II protein expressed influences presentation of antigens to immune cells and how an immune response may be initiated
- CD14 → a monocyte receptor for endotoxins (LPS) which could influence an individual’s immune response to antigens
- Susceptibility locus for asthma is on chromosome 5q → near a gene cluster for IL-3, IL-4, IL-5 and IL-13
- Polymorphisms for the IL-13 gene have the strongest association with asthma or allergic disease
- Polymorphisms in ADAM33 on chromosome 20q → metalloproteinase linked to increased proliferation of bronchial smooth muscle cells and fibroblasts which contribute toward bronchial hyperresponsiveness and subepithelial fibrosis

Epidemiology

- 150,000,000 sufferers worldwide
- 5,400,000 sufferers in the UK in 2014
- Affects 1 in 11 children and 1 in 11 adults in the UK
- Every 10 seconds, someone in the UK has a potentially life-threatening asthma attack
- 3 people die a day from an asthma attack in the UK

Pathogenesis

Asthma is a chronic disorder of the conducting airways, usually caused by an immunological reaction, marked by episodic bronchoconstriction due to increased airway sensitivity to a variety of stimuli, inflammation of the bronchial walls and increased mucus secretion.

Asthma flare ups are generally caused by IgE mediated type I hypersensitivity reactions following exposure to environmental allergens in a genetically predisposed person. Upon entry into the body, inhaled allergens are taken up by dendritic cells and presented to T helper cells, inducing an abnormally exaggerated Th2 response to a normally harmless environmental antigen.

Th2 cells produce a number of cytokines:
IL-4 → stimulates proliferation and differentiation of plasma cells and IgE production
IL-13 → stimulates mucus secretion from bronchial submucosal glands and IgE production from plasma cells

IgE antibodies produced by plasma cells bind to the Fcε receptors on submucosal mast cells. On repeat exposure to the allergen, allergen binds to these mast cell bound IgE immunoglobulins, cross linking the Fc receptors on mast cells. This triggers mast cell degranulation and the release of:

- Leukotrienes → bronchoconstriction, increased vascular permeability and oedema and increased mucus secretion (B4 recruits immune cells, C4, D4, E4 bronchoconstrict)
- Histamine → potent bronchoconstrictor
- Prostaglandin D2 → bronchoconstriction and vasodilation (causing oedema)

These features characterise the early phase response in which there is bronchoconstriction, increased mucus production and increased vascular permeability and oedema, leading to symptoms of wheezing, chest tightness and breathlessness. Mast cell contents also activate subepithelial vagal receptors, triggering acetylcholine release from vagal efferents that directly induces smooth muscle contraction through muscarinic receptors.

In the late phase response, Th2 cells release IL-5 which activates locally recruited eosinophils into the airways. These cells also bind to IgE immunoglobulins through their Fcε receptors, which are cross linked when bound to the allergen. Eosinophils release eosinophil cationic protein and major basic protein which damages cells of the respiratory tract and leukotrienes causing oedema and further bronchial constriction. This inflammatory response is perpetuated by chemokines produced by T and epithelial cells which recruit more T cells, eosinophils, basophils and monocytes to the area. Epithelial cells also release eotaxin which is another chemokine for eosinophils. Although Th2 are the predominant T cell type in asthma, Th17 cells play an important role in recruiting neutrophils to the site of inflammation.

Chronic inflammation leads to bronchial hyperresponsiveness to substances such as histamine, cold air, sulphur dioxide and AMP. This is mediated by the high levels of circulating IgE which makes the airways more responsive to contractile stimuli. Epithelial shedding that results from chronic inflammation exposes subepithelial tissues to inflammatory derived mediators and also sensitises nerves, causing altered neural control of the airways.

Airway obstruction results from muscular bronchoconstriction, acute oedema and mucus plugging. Repeated exposure to the allergen and immune reactions eventually leads to airway remodelling, in which there are permanent structural changes to the respiratory tree.

**Types of Asthma**

Asthma can broadly be split into atopic and non-atopic categories. Atopic asthma is the most common type, caused by a type I hypersensitivity reaction. It involves allergic sensitisation and these patients often have a family history of asthma and a high serum IgE. Non-atopic asthma is usually triggered by infection.

- **Drug induced asthma**
  - Occurs in 3-5% of asthmatic patients

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ASTHMA – DISEASE SUMMARY

- Sensitivity to NSAIDs and aspirin
- Can cause urticarial as well as typical asthmatic symptoms
- Drugs which inhibit the arachidonic acid pathway inhibit the production of prostaglandins. Prostaglandin E inhibits enzymes that generate leukotrienes, so inhibition of this causes an upregulation of leukotrienes, which causes bronchoconstriction.

- **Seasonal asthma**
  - Occurs at certain times in the year, depending on the allergen

- **Cold/exercise induced asthma**
  - Non-atopic
  - Airway cooling causes dehydration of the fluid lining the respiratory epithelium. Drying of the airways causes increased blood flow (hyperemia) leading to oedema and bronchoconstriction.
  - With exercise induced asthma, symptoms generally occur 5-15 minutes after exercise, as catecholamine release during exercise helps with bronchodilation

- **Stress induced asthma**
  - At first, catecholamine release causes bronchodilation
  - After long periods of exposure to catecholamines, their receptors become downregulated causing their effects to be less severe
  - Reduction in catecholamine sensitivity also reduces immune cell regulation, as T and B lymphocytes possess adrenergic receptors, so catecholamines can regulate IL-4, IL-5 and IL-13 expression, histamine release from mast cells and recruitment and activation of eosinophils

**Signs & Symptoms**

- **Breathlessness which is worse at night**
  - Airway obstruction due to bronchoconstriction and mucus plugging → respiratory muscles need to work harder to generate a negative intrapulmonary pressure with respect to atmospheric pressure in order to allow inspiration → muscle fatigue may lead to breathlessness
  - Inability to draw in as much air due to bronchoconstriction
  - Increased exposure to allergens at night; cooling of the airways; being in a reclined position leading to pooling of secretions worsens airway obstruction at night, leading to worse breathlessness
  - Cortisol peaks in the early morning hours, leading to increased inflammation

- **Episodic symptoms that may become persistent with time**
  - Episodic symptoms suggests that the condition is triggered by exposure to an allergen
  - Persistent mucosal inflammation → upregulation of nerves, vessels and glands in respiratory tract → increased responsiveness to allergens and environmental irritants (also epitope spreading) → patient becomes sensitive to a wide range of stimuli, causing their symptoms to become persistent

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• **Inspiratory and expiratory wheezes**
  o Inflammation of the conducting airway mucosa → contracted airways have increased mucosal folds → increased airway resistance and turbulent flow → wheeze sound

**Histological Features**

Repeated exposure to allergen and chronic immune reactions leads to airway remodelling. This is primarily caused when asthma associated inflammation becomes chronic and neutrophils release enough proteases and eosinophils release enough MBP etc. which damage epithelial cells and elastic fibres in bronchial walls, leading to growth factor release and fibrosis which causes permanent airway narrowing and irreversible deterioration of lung function.

- Hypertrophy and hyperplasia of bronchial smooth muscle
- Epithelial cell injury
- Increased airway vascularity → oedema
- Subepithelial mucus gland hypertrophy
- Increased numbers of goblet cells
- Nerve proliferation
- Fibrosis → subepithelial collagen deposition

**Investigations**

The following can be used to rule out other conditions:

- **Respiratory rate** → heart disease and infection would cause tachypnoea
- **Heart rate** → tachycardia may indicate infection or heart disease
- **Blood pressure & jugular venous pressure** → rules out heart failure. JVP is an indirect measure of central venous pressure and if raised may indicate heart failure, constrictive pericarditis or fluid overload
- **No peripheral oedema** → could rule out heart failure
- **Blood tests** → could rule out anaemia and infection. In some asthmatic patients you may notice abnormal eosinophil and IgE counts
- **Sputum** → clear indicates no infection

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- **Respiratory function tests**
  o Reduced FEV1 and FVC suggests airway obstruction as patient cannot exhale air from the lungs at a fast rate due to obstruction
  o Reduced FEV1/FVC ratio (<70%) → FEV1 reduced more than FVC because total lung volume is unaffected, but patient cannot exhale air quickly in the first second due to collapsing of the conducting airways
  o Reduced PEF
  o Poor spirometry tests are improved after taking a beta agonist → airway obstruction is reversible
- **Skin test & RAST (radioallergosorbent test)** → can detect allergies to particular triggers

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Differential Diagnosis

Asthma may be hard to differentiate from COPD. Features of asthma include:

- Diagnosed at a younger age
- Evidence of allergic reaction to a particular trigger → positive skin test/RAST and episodic symptoms
- Flare ups are acute in onset
- FEV1/FVC <70% indicative of airflow obstruction → along with symptoms that are at least partially reversible with a beta agonist

Management & Treatment

Management aims to relieve bronchoconstriction, reduce mucous secretion and suppress airway oedema. Prevention is used to inhibit bronchoconstriction, suppress chronic inflammation and inhibit airway remodelling.

Initially just an inhaled beta-2 agonist is taken when needed. For persistent cases an inhaled steroid can be added. A long-acting beta agonist may be added in more moderate cases and oral prednisolone may be given in severe asthma.

Patients generally take preventer inhalers of either a steroid and/or a long acting beta agonist such as budenoside/beclametasone and salmeterol. These can pre-empt bronchoconstriction that may occur upon exposure to an allergen and also prevent symptoms flaring up overnight. Relievers can be taken which can be used in case of a flare up and these are short acting beta agonists such as salbutamol. All of these medications are inhaled through an inhaler, of which there are many types.

In severe asthma, oxygen therapy may be used to treat hypercapnia associated with air trapping and inefficient ventilation that may occur following chronic asthma with airway remodelling. Bronchodilators are generally delivered via nebuliser, as these allow larger doses to be given and more rapid delivery. IV steroids are also given as they have a greater bioavailability and rapidly combat inflammation. Fluid therapy can help rehydrate dehydrated airways following an asthma attack.

In a life-threatening asthma attack, nebulised muscarinic antagonists (ipratropium), IV aminophylline (phosphodiesterase inhibitors) and beta 2 agonists may be used along with assisted ventilation.

Long Term Effects

Nearly one half of children diagnosed with asthma have a reduction in symptoms and require less treatment by late adolescence or early adulthood. Patients who are diagnosed at an older age tend to have more chronic symptoms.

Patients with poorly controlled asthma develop long term changes due to airway remodelling, leading to chronic symptoms and a significant irreversible component to their disease. End stage asthma can result in irreversible airflow obstruction just like COPD.
Mortality from asthma is mainly related to poor lung function and poor asthma management. Other factors include being over 40 years old, having a cigarette pack history of over 20 years and having a FEV1 of 40-69% the predicted value.

**Additional Points**

The atopic triad consists of asthma, atopic dermatitis (eczema) and hayfever. All of these are linked with Th2 mediated immunity. They all share similar risk factors and patients often have more than one of the conditions.

The primary inflammatory cells involved in asthma are CD4+ T cells, B cells, mast cells and eosinophils, compared to COPD in which the inflammatory response to tobacco smoke is mainly neutrophilic and monocytic.

**Breathlessness →**

Viruses can trigger non-atopic asthma attacks. Certain viruses can block the function of inhibitory autoreceptors on presynaptic vagal efferents innervating the respiratory tract. Blocking of these autoreceptors prevents them from inhibiting the release of acetylcholine across the synaptic cleft. The resulting acetylcholine released, acts on M3 receptors on bronchial smooth muscle cells, leading to bronchoconstriction.

**Acute Severe Asthma Attack**

- Unable to speak freely
- Pulse >110bpm
- PEFR <50% predicted
- Severe hypoxaemia (pO2 <8kPa) with normo- or hypercapnia (pCO2 >5kPa)

Give oxygen (40-60%), nebulised salbutamol, IV hydrocortisone or oral prednisolone (high dose) to reduce oedema in walls of the airways). Note that hydrocortisone has a short duration of action, a lower glucocorticoid potency than prednisolone and 4 times greater mineralocorticoid receptor activity compared to prednisolone.

**Life-Threatening Asthma Attack**

- No breath sounds
- Cardiovascular depression (bradycardia or hypotension)
- PEFR <33% predicted
- Confusion/coma

Give nebulised ipratropium, IV aminophylline or salbutamol, magnesium sulphate and assisted ventilation.

**Notes on Breath Sounds**

Normal breath sounds are from central areas in the upper respiratory tract (trachea and bronchi) → caused by turbulent flow through these airways due to high degree of branching; they occur down
to the 15th division of the respiratory tree and may be affected when these central areas shift, such as in mediastinal shift due to tension pneumothorax

Wheeze \(\rightarrow\) inflamed bronchi have more mucosal folds \(\rightarrow\) turbulent flow due to increased resistance to airflow through constricted airways causes wheeze

Crackles/crepitations \(\rightarrow\) heard on inspiration due to popping open of small airways which are collapsed by fluid or exudate

Pleural rub \(\rightarrow\) grating noise caused when the visceral and parietal pleura rub against each other \(\rightarrow\) can occur if one or both layers are inflamed such as in pneumonia \(\rightarrow\) they appear on inspiration and expiration

Stridor \(\rightarrow\) high pitched sound caused by turbulent airflow through a partially obstructed airway in the larynx or lower in the bronchial tree \(\rightarrow\) can be inspiratory or expiratory but usually heard on inspiration \(\rightarrow\) can be caused by foreign bodies, tumour, infection or oedema

**Why do People Die from Asthma?**

Despite the facts asthma should be treatable and reversible, 3 people die each day in the UK from asthma attacks.

- Inadequate treatment with steroids and poor self-monitoring of asthma
- Patient didn’t realise how severe their attack is and don’t do anything about it
- Brittle asthma \(\rightarrow\) type 1 is characterised by sustained chronic variability of PEFR; type 2 is characterised by sudden unpredictable drops in PEFR where asthma symptoms are otherwise well controlled. It applies to 5% of cases – these are unstable cases that don’t respond to maximal inhaled treatment. In both types of brittle asthma patients are subject to severe recurrent attacks.

**NICE GUIDELINES ON ASTHMA TREATMENT**

- Explain that lifestyle changes and medication are meant to control asthma symptoms and prevent an exacerbation
- Explain the difference between reliever and preventer therapy and demonstrate how to use inhalers and spacer devices
- Prescribe an effective delivery device on the basis of convenience, cost and suitability
- Prescribe a short acting beta 2 agonist for use as required to treat daytime symptoms (twice weekly or less often) of short duration (lasting only a few hours)
- Prescribe a regular inhaled corticosteroid with the short acting beta agonist if symptoms are at least three times a week or waking the person one night weekly
- Prescribe a peak flow meter, record the person’s best expiratory flow rate reading and advise monitoring during an exacerbation, worsening symptoms, or a medication change. Regular monitoring of peak expiratory flow is no longer advised as it does not provide additional benefit when added to a symptom based management strategy