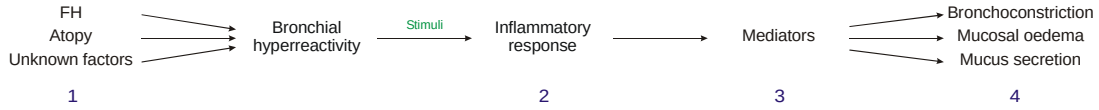
Asthma

BTS/SIGN guidelines
- Full: Thorax 2003; **58** (Suppl 1)
- Summary and November 2005 update: from BTS website www.brit-thoracic.org.uk

A chronic inflammatory disorder of the airways, associated with
- Airway hyperreactivity
- Widespread but variable airflow limitation, often reversible

Pathophysiology

Due to bronchial hyperreactivity, stimuli such as AIDEECS[1] precipitate bronchoconstriction, mucosal oedema and mucus secretion (maladaptive response), leading to the clinical picture of variable airflow limitation.



Disease modification
- 1: avoid AIDEECS, omalizumab
- 2: steroids
- 3: cromoglycate, leukotriene antagonists – remember redundancy

Symptomatic relief
- 4: β_2-agonists, antimuscarinics

Successful treatment of the underlying inflammatory process (1, 2, 3) will improve symptom profile, quality of life, reduce bronchodilator requirement and airway wall remodelling (4).

Hx/Ex/Ix

Hx
- Sx episodic, variable
  - Wheeze
  - SOB
  - Chest tightness
  - Cough
- Patterns and severity of symptoms and exacerbations
- Recognised triggers
- Personal Hx or FH of atopy
- Use of NSAIDs/β-blockers – worsening of symptoms?

Ex
- None – common
- Wheeze
- Tachypnoea
- Also look for: atopic eczema, nasal polyps (esp. in aspirin-sensitive asthma)

Ix
- >20% diurnal variation on ≥3 days/week for 2 weeks on PEF diary
  - Or FEV_1 ≥15% (and 200ml) increase after short-acting β_2-agonist
  - Or FEV_1 ≥15% (and 200ml) increase after trial of PO steroids (prednisolone 30mg for 2w)
  - Or FEV_1 ≥15% (and 200ml) decrease after six minutes of exercising

[1] Allergens, infection, drugs, exercise, emotion, cold air, smoking

- Histamine or methacholine challenge in difficult cases
- Assessment of atopy: skin prick tests, ↑total IgE, RAST[2]

Associations
- GORD, PAN, Churg-Strauss, ABPA

Non-pharmacological management

Primary prevention
- Avoid smoking in pregnancy
- Breast feeding
- Allergen avoidance

Secondary prevention
- Allergen avoidance
- Quit smoking
- Weight reduction

(No evidence base for any others.)

Pharmacological management

Summary of drug therapy of chronic asthma

BTS advocates stepwise management.
- **Step 1** – mild intermittent asthma
  - Short-acting β_2-agonist as required
- **Step 2** – regular preventer therapy
  - Add regular inhaled steroid (200-800μg/day - 400μg usually an appropriate starting dose)
    - If exacerbations in last two years
    - If using β_2-agonist ≥3 times/week
    - If symptomatic ≥3 times/week, or waking one night a week
- **Step 3** – add-on therapy
  - Add regular long-acting β_2-agonist (LABA)
  - Assess control of asthma
    - Good response: continue LABA
    - Inadequate response: continue LABA, increase inhaled steroid to 800μg/day
    - No response: stop LABA, increase inhaled steroid to 800μg/day; if control still inadequate, consider trial of e.g. leukotriene antagonist or SR theophylline
- **Step 4** – persistent poor control
  - Consider trials of
    - Increasing inhaled steroid up to 2000μg/day
    - Addition of a fourth drug, e.g. leukotriene antagonist, SR theophylline, oral β_2-agonist
- **Step 5** – continuous or frequent use of oral steroids
  - Use daily steroid tablet in lowest dose providing adequate control
  - Consider other treatments to minimise the use of steroid tablets
  - Refer patient for specialist care

Teach and check inhaler technique
Prescribe PEFR meter and ask to keep diary

[2] Indicative of exposure but no correlation with Sx

Goals of Treatment

↓morbidity – symptomatic control and prevention of exacerbations with minimal SEs
↓mortality – treat exacerbations early to prevent them from becoming severe

- Start treatment at the step most appropriate to initial severity
- Achieve early control
- Maintain control by
    - Stepping up until asthma controlled, i.e.
        - Minimal symptoms during day and night
        - Minimal need for inhaled β_2 agonists
        - No exacerbations
        - No limitation of physical activity
        - Normal lung function (FEV_1 and/or PEFR>80%)
        - Minimal SEs from medication

- Before initiating new drug therapy
    - Check compliance with existing therapies
    - Check inhaler technique
    - Eliminate trigger factors

- Stepping down when control is good
    - Maintain on lowest possible dose of inhaled steroid
    - Consider reductions every 3m, decreasing the dose by approx. 25-50% each time

Drug administration by inhalation

Is the preferred route of administration. Enables small doses to be used and hence reduce systemic side-effects. Drugs are in a particulate form with an optimum particle size of 2 microns (large particles deposit in the mouth and small ones fail to deposit in the distal airways). Some drugs such as leukotriene receptor antagonists and theophylline cannot be given by inhalation.

Pressurised metered dose inhaler (pMDI)

- Drug dissolved in a low boiling point liquid in pressurised canister
- Metered dose is ejected and solvent instantly vaporises
- CFCs being replaced by HFAs (hydrofluoroalkanes) – if switching, dose may require adjustment
- May be difficult to co-ordinate inhalation and activation
    - Teach technique: shake inhaler, fire inhaler shortly after start of slow full inspiration, hold breath for 10s
    - Consider using breath-actuated inhaler, dry powder inhaler, Haleraid device (responds to squeezing – for e.g. arthritic patients), spacer

Dry powder inhaler (DPI)

- Drug is formulated as a micronised powder, which is released by inspiratory airflow
- Low PEFR (<60) can be a problem
- Can cause cough and transient bronchoconstriction

Spacers

- Increase the fraction of droplets in the effective range
- Need to match inhaler to spacer

- Less pharyngeal deposition – less oral candidiasis and dysphonia with steroids (use routinely for steroid doses >800μg/day)
- Tidal breathing as effective as deep breaths

Nebuliser

- Convert a solution or suspension of drug into an aerosol
    - Jet nebulisers produce droplets by a stream of air or oxygen
    - Ultrasonic nebulisers produce droplets by vibration
- Delivered by face mask
- Requires no co-ordination and can deliver bigger doses of drug (about 10-fold higher)

Individual drug classes

Beta-2 agonists

Short-acting	salbutamol (Ventolin®)
	terbutaline (Bricanyl®)
Long-acting	salmeterol (Serevent®)
	formoterol

Mechanism

- ↑G_s – ↑cAMP – active bronchodilatation
    - Interesting oddity: lungs are not sympathetically innervated – only receptors
- Extremely effective by multiple routes (inhalation, nebulisation, orally (tablet or liquid) and IV)

Adverse effects

- β_2: tremor, hypokalaemia
- β_1: tachycardia and palpitations
- Occasional hypersensitivity reactions (esp. salmeterol)
- Minimised by topical administration via inhaler/nebuliser

Note

i) Can be used safely in pregnancy by inhalation/nebulisation (β_2 agonism causes relaxation of uterine smooth muscle – tocolytic)

ii) LABAs can be used to give continuous 24h cover when given twice daily by inhalation
    - Structurally, salmeterol is salbutamol with a long CHO chain; retained within cell membrane and comes on and off the receptor
    - Should never be used without a corticosteroid since it can mask deterioration until serious and β_2-agonist unresponsive
    - Some evidence that sensitivity to salbutamol is reduced

Antimuscarinics

E.g. ipratropium bromide (Atrovent®)

Mechanism

- Competitive inhibition of vagal cholinergic nerve endings (M_3) – vagolytic
- ↑$G_{q/11}$ – ↑IP_3/DAG – bronchodilatation by blocking constriction, hence less effective
- Results in relaxation of bronchial smooth muscle
- Given by inhalation or nebulisation

Adverse effects

- Dry mouth
- Glaucoma
- Occasionally, systemic anticholinergic effects (despite being poorly absorbed quaternary ammonium derivatives, cf. easily absorbed tertiary derivatives, e.g. atropine)
- Prostatic hypertrophy

Note

Less effective in asthma than β_2 agonists

- Opposing only one physiological constrictor mechanism rather than directly bronchodilating
- High vagal tone usually only in acute asthma, hence less effective in chronic setting
- Blockade of presynaptic M_2 receptor may stimulate neuronal ACh release
- Main use in COPD patients who do not respond to β_2 agonists

Corticosteroids

Inhaled/nebulised	beclomethasone (Becotide®/Becloforte®/Qvar®)
	budesonide (Pulmicort®)
	fluticasone (Flixotide®) – most potent, use half the dose of beclomethasone/budesonide
Oral	prednisolone
Oral/IV	hydrocortisone

Mechanism

- Reduce influx of inflammatory cells
- Reduce release of mast cell mediators

- Reduce microvascular leakage and oedema

Adverse effects
Inhaled therapy causes little systemic exposure, and thus avoids side-effects by spatial rather than pharmacological specificity
- Cough
- Oral candidiasis (rinse mouth after use)
- Dysphonia
- Possible growth suppression in children
- Systemic effects possible with very high doses (if high doses used for prolonged periods, should carry steroid card)

Chronic oral prednisolone administration can cause Cushing's syndrome

Note
- As with other inhalers, approx. 90% of the inhaled dose is swallowed
- Synthetic steroids are designed to show high first-pass metabolism

Leukotriene antagonists
E.g. montelukast, zafirlukast

Mechanism
- Competitive antagonists of LTD_4
- Thus are anti-inflammatory and bronchodilators

Adverse effects
- Rare
- Churg-Strauss syndrome

Note
- Effective in aspirin induced and exercise-induced asthma
- 5-lipoxygenase inhibitors (e.g. zileutin) have been withdrawn

Methylxanthines
Oral theophylline (MR: nuellin, uniphyllin)
Oral/IV aminophylline (MR: phyllocontin)

Mechanism
- Is still a subject of debate
    - Relaxation of bronchial smooth muscle
        - PDE inhibitor
        - Competitive adenosine receptor antagonist
    - CNS effect: ↑diaphragmatic contractility
    - Disease modifying action in chronic use
- Can be administered orally or IV (suppositories withdrawn due to proctitis)

Adverse effects
- β_2: hypokalaemia (esp. when combined with β_2 agonists)
- β_1 (non-selective action): tachycardia, palpitations, arrhythmias
- Nausea and abdominal disturbances
- Headache
- Convulsions – hence CI in epilepsy
- Narrow therapeutic index – need to measure levels on oral therapy to get optimum dose for efficacy without side-effects and on parenteral administration to prevent cardiac/CNS risk
- P_{450} catabolism → many interactions
    - Smoking and barbecued meat increase clearance, as well as the usual enzyme inducers

Note
Aminophylline is a mixture of theophylline and a solubilising agent.

Cromoglycate and related therapy
Sodium cromoglycate (intal)
Nedocromil (tilade)

Mechanism

- Suppression of early and late inflammatory responses (mast cell stabilisers)
- Possible bronchodilator action
- Can be given by inhalation or nebulisation

Adverse effects

- Cough, transient bronchospasm and throat irritation

Note

- No longer part of BTS management guidelines; there is evidence that cromoglycate is ineffective in children, and evidence for nedocromil is limited to age 5-12
- Were only useful prophylactically – cannot prevent action of mediators that have already been released
    - Extrinsic allergic asthma
    - Exercise induced asthma

Inhaler 'colour code'

- Blue salbutamol, terbutaline
- Grey ipratropium
- Brown beclamethasone, budesonide
- Orange fluticasone
- Burgundy beclamethasone 250 (Glaxo)
- Green salmeterol, phenoterol (Oxis)
- Purple seretide (= serevent/ipratropium + flixotide)
- White/red symbicort (= pulmicort + Oxis)

New treatments under evaluation

- Immunosuppressants
    - Cyclosporin, tacrolimus
        - Toxicity limits use to investigational role in steroid-resistant asthma
    - Methotrexate
        - Anti-inflammatory effect in low doses
        - Use limited to severe resistant cases in specialist units, due to high toxicity
    - Anti-IL-5 and IL-12
        - Both reduce eosinophil counts but may not offer clinical benefit
- Immunomodulation
    - Omalizumab, and anti-IgE, decreases Sx score and β_2-agonist use[3]
    - BTS/SIGN: "May be of benefit in highly selected patients with severe persistent allergic asthma, but at present its role in the stepwise management of asthma is unclear."
- Mediator antagonists
    - PAF antagonists
    - Cytokine antagonists
- Bronchodilators
    - Single enantiomer salbutamol - (R)-salb is the active enantiomer; (S)-salb inactive, metabolised 10-fold slower and can increase airway hyperresponsiveness
    - Inhibitors of specific PDE subtypes e.g. PDE-4 (predominant isoform in inflammatory cells; potential for fewer side-effects vs. theophylline)
    - Potassium channel activators

Effectiveness of anti-asthma therapy

1. Most patients have mild disease and can remain symptom free on standard drug therapy.

[3] BUSSE, W. ET AL. (2001): Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* **108**:184-90.

2. Key to management is the aggressive treatment of inflammation and hence prevention of acute episodes and prompt treatment of such episodes when they occur.

3. A minority of patients have resistant asthma with significant morbidity despite full medical therapy.
    - New drugs in development may produce further improvement in morbidity for the minority of resistant asthmatics but are unlikely to have a significant impact on the management of acute severe asthma.
    - A subset (1-5%) of patients have glucocorticoid resistant asthma. These patients tend to be at the more severe end of the disease spectrum and may have a defect in biochemical response to glucocorticoid e.g. failure of glucocorticoid to suppress T-cell proliferation.

4. Deaths from asthma still occur and 80% are preventable
    - Failure to recognise deterioration in control prior to hospital admission
    - Inappropriate management prior to admission
    - Inappropriate management of in-patient

    - Above caused by
        - Failure to appreciate severity of illness (patient/relative/doctor)
        - Inadequate objective measurements (PEFR/SaO_2/ABG)
        - Inadequate drug therapy and under-treatment with systemic steroids
        - Inadequate specialist input*

* It is well recognised that in-patient management by a specialist respiratory physician is associated with
- Lower in-patient mortality
- Lower post-discharge morbidity

Important concepts in development of new anti-asthma agents

Potency
Amount by weight of drug in relation to therapeutic efficacy.

Is not usually of great importance. Drugs in asthma are often given by inhalation and there is a limit to how much can be given by this route. New inhaled therapies need to be of sufficient potency for them to be able to be packaged in aerosol or dry powder forms and administered in sufficient doses to be efficacious. The new inhaled steroids are extremely potent.

Efficacy
Pharmacological
Strength of response induced by occupancy of a receptor by an agonist

Therapeutic
The therapeutic effectiveness of an agent, referring to the maximum such effect that can be elicited. The efficacy may refer to a biological marker e.g. change in peak flow or an 'end-point' such as admissions with acute asthma or asthma deaths. New agents need to demonstrate superior efficacy without worsening side-effects in diseases for which there are alternative acceptable treatments. This usually relates to better symptom control or better efficacy in a subgroup of resistant patients.

Example: the leukotriene antagonists are efficacious in aspirin-induced asthma and exercise induced asthma. They also have a steroid sparing effect. They thus help maintain control but enable a better side-effect profile.

Tolerability
Refers the side-effect profile of the medication rather than life-threatening problems. Such issues do not raise a safety concern (medications that are not safe do not get registered) but have a major impact on patient compliance.

Example: the newer inhaled steroids such as flixotide. These have very high (almost 100%) hepatic first pass metabolism and hence very little systemic exposure, tolerability is therefore good. New agents in asthma need to be very well tolerated since very effective, well tolerated treatments are already available.

Pharmacokinetic profile
Relates to rate at which a therapeutic effect can be produced and the rate at which that effect wears off i.e. rate of absorption, distribution, metabolism and excretion. Remember that pharmacokinetic and pharmacodynamic profile of a drug may be different.

Example: salmeterol has a much longer half-life than salbutamol. This enables twice daily administration and evening out of variation in peak-flow. Salbutamol has a short half-life since it need only be given for immediate symptomatic relief. Long half-lives are important for oral prophylactic treatment since they provide stable 24h blood levels and reduced frequency of administration (improves patient compliance)

Cost

The cost of new medicines is an increasing problem for the health service. It costs about $800 million to develop a new drug plus the costs of all those drugs that don't make it to market. New drugs must therefore demonstrate superior efficacy and tolerability or they will not be used due to the cost differential over older cheaper drugs

Specific subtypes of asthma

Aspirin-sensitive asthma

- Up to 10% of chronic severe asthmatics are aspirin intolerant
- Associated with nasal polyps
- Thought to be due to an abnormality of arachidonic acid metabolism and is a class effect of COX-Is such as NSAIDs
- Inhibition of COX prevents prostaglandin production but leukotrienes are still produced via 5-lipoxygenase
- Leukotriene inhibitors are particularly effective here

Exercise-induced asthma

- Up to 80% of asthmatics bronchoconstrict after exercise or hyperventilating cold air
- May be only symptom in young, mild asthmatics
- Probably relates to drying of airways resulting in mast-cell degranulation
- Refractory period of 2-4h where subsequent exercise causes much less Sx
- β_2-agonists preventative
- Leukotriene antagonists effective

- Often an expression of poorly controlled asthma – regular treatment should be reviewed

Extrinsic or allergic asthma

- Brought on by external factors
- Commonest allergen = mites
- Particularly common in children

Intrinsic or non-allergic asthma

- Non-specific triggers such as exercise, emotion, or drugs
- More common in adults

Occupational asthma

- More common in atopic individuals
- Caused by sensitising agents, not non-specific triggers or temporary irritants (e.g. chlorine)
- Causes
    - High molecular weight: lab animals (urine proteins), wood dust, flour, grains, proteolytic enzymes (biological detergents)
    - Low molecular weight: isocyanates (paint, insulation), platinum salts (refineries), epoxy resins, glutaraldehyde, acid anhydride, soldering flux
- Initially asymptomatic, but features develop within 2y of first exposure
- Detection: PEFR at home/work, RAST, bronchial provocation testing

Brittle asthma

- Very little or no warning of acute attacks. Often asymptomatic between attacks. Dangerous but rare.

Nocturnal asthma

- May suffer at night and be asymptomatic during the day. Indicates poor control.

Cardiac asthma

- A popular term of a syndrome caused by heart failure – not to be confused with actual asthma!

Acute asthma

See BTS posters for acute asthma in hospital setting.

Aim: ↓mortality

Note

- Steroids
  - Oral prednisolone works as quickly as IV hydrocortisone but latter may have more of a placebo effect in terms of calming and reassuring the patient
- Other meds
  - IV magnesium now used routinely before IV aminophylline or IV salbutamol
    - *Aminophylline:* given as a loading dose over 20min and followed by a continuous infusion. If patient already on oral theophyllines, check blood levels or use salbutamol.
    - *Salbutamol:* can be used if on oral theophyllines or history of epilepsy.
  - Check potassium prior to starting infusions in view of risk of hypokalaemic arrhythmias.
  - Antibiotic therapy in acute asthma only if signs of bacterial infection. More useful in COPD patients.
- ABGs
  - Pure asthmatics are usually hypoxic and hypocarbic (hyperventilation blows off CO_2). Normal or high CO_2 suggests that the patient is tiring and is a very bad sign.
- CXR
  - Not routinely, but if clinical consolidation or pneumothorax, or if NIPPV considered