

Asthma and Atopic Eczema

Presenting Signs and Symptoms:

- Wheeze
- Chest tightness
- Shortness of breath
- Rapid breathing
- Dry or productive cough

Epecially characteristic if the symptoms are

- Recurrent
- Worse at night or early morning

Obviously triggered by **exercise, irritants, allergens or viral infection.**

NOTE- Do not rely solely on the presence of wheezing or other airway sounds to diagnose asthma. Airflow limitation in smaller airways can cause such severe obstruction that wheezing is not noticeable. Patients in this state usually have other physical signs reflecting severity, such as cyanosis, drowsiness, difficulty speaking, tachycardia, and chest hyperinflation.

Severe asthma may present with

- Appearance of exhaustion and fear
- Inability to speak
- Lethargy due to hypercapnea
- **Obvious cyanosis (red flag: heading for trouble!)**
- Palpitations due to tachycardia

Differential Diagnosis

- Chronic bronchitis,
- emphysema,
- pneumonia,
- neoplasm,
- cystic fibrosis,
- localized obstruction of the airways,
- infection/infestation,
- laryngeal dysfunction,
- gastroesophageal reflux

Grading of Dyspnoea:

- **I = on heavy exertion**
- **II = moderate exertion**
- **III = minimal exertion**
- **IV = at rest**

History

What to look for in the history:

- **Current symptoms:**
 - **severity** (exercise limitation? Sleep disturbance? How often do they wake up at night?)
 - **duration**
 - **aggravating factors- ALLERGY? Is there ECZEMA? Very important**
 - **Allergic rhinitis? Hay fever?** Pt may not identify hay fever with allergy
- **?Current medications unrelated to asthma?-beta-blockers or aspirin?**
- **Pattern of symptoms** (chronology of the illness over days/weeks)
- **Quality of Cough** and any sputum thus produced
- **Present management** and its perceived effect
(eg, how often is the puffer used, how many puffs are needed, how long does a puffer last, how it is used (properly?), etc)
- **Previous hospitalisation** (due to a chest complaint? Allergic reaction? ICU stay?)
- **Home and work environment** (?dust, pollen, pets, chemicals? Are they a florist or veterinarian? Current smoker or lives with smokers? Do the symptoms improve on the weekends?)
- **Impact of disease on lifestyle** (including ADLs, eg. cooking, cleaning, shopping, transport; as well as recreational activities, and work duties –i.e how much work/school is missed due to asthma)
- **Family history** of atopy- rashes, asthma, anaphylaxis?

Findings on Examination

VITALS:

- RESPIRATORY RATE: **ELEVATED**
- PULSE: **ELEVATED**
- TEMPERATURE: **Normal**, ruling out Infection

LOOK / FEEL:

- **Tracheal Tug**: displacement of trachea downwards with respiration
- Use of **accessory muscles**
- **Intercostal + Subcostal Recession**
(deep grooves become apparent between ribs each time the patient inhales)
- **Respiratory Paradox**
- **Liver** may be appreciably below costal margin, esp. in young children
- **Eczema** may be present

AUSCULTATION

- **Audible wheeze.**
- **Reduced air entry- bilaterally**
- **bilateral inspiratory crackles and expiratory wheezes**

OXIMETRY decreased, suggesting poor ventilation

Tests and Investigations

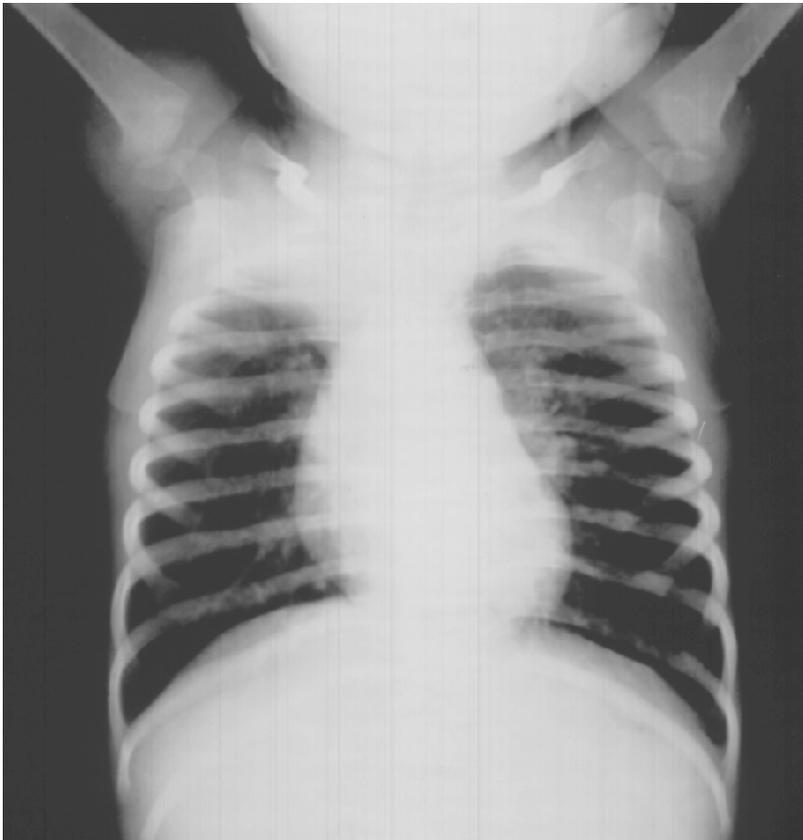
Full blood count

- EXPECTING NORMAL but run test anyway to eliminate infection
- May have mild basophilia

Chest X-ray

- **HYPERINFLATION is the ONLY EXPECTED SIGN;**
- **May have** some collapse or consolidation due to overabundance of secretions
- use the CXR to **ELIMINATE ASPERGILLOSIS OR PNEUMONIA**

Below: pediatric CXR showing hyperinflation with partial collapse/consolidation of right upper lobe.



In a hyperinflated chest radiograph, **more than six ribs** can be seen **above the diaphragm** in the mid-clavicular line. There are also flat hemidiaphragms

ALLERGEN SKIN TEST:

1. Skin prick testing is most commonly performed on the forearm, although the back is sometimes used.
2. The arm is first cleaned with alcohol,
3. a drop of commercially-produced allergen extract is placed onto a marked area of skin.
4. Using a sterile lancet, a small prick through the drop is made.
5. This allows a small amount of allergen to enter the skin.

If you are allergic, a small mosquito-like lump will appear at the site of testing over 15-20 minutes.

6. MEASURE THE WELT for an objective record of the reaction

Sensitivity and specificity is BETTER THAN R.A.S.T.

Skin tests are slightly uncomfortable, but is usually well tolerated and accurate, even in small children and infants.

NASOPHARYNGEAL ASPIRATE CULTURE:

1. to determine which pathogen may have precipitated the attack, if rhinitis (any U.R.T.) preceded asthmatic episode. Not very useful, as by the time the episode presents the horse has already bolted.
2. To measure the number of **EOSINOPHILS** in nasal mucus:
their numbers will **INCREASE in an ALLERGIC REACTION**

RAST BLOOD TESTING: *RADIOALLERGOSORBENT TEST*

= MEASUREMENT OF ALLERGEN-SPECIFIC **IgE**

- In general, **it is less likely to accurately detect allergies** than the skin test,
- only performed **when skin testing is not easily available,**
- **when skin condition** prevent accurate testing (eg.severe eczema or dermatographism)
- or when the patient is taking **medications that interfere with accurate testing.** (such as antihistamines or tricyclic antidepressants)

LUNG FUNCTION TESTS

(unless patient is too young to conduct these tests)

Spirometers measure vital capacity, forced vital capacity, and timed measurements such as the forced volume of air that can be expired in 1 second (FEV1), which is the best single measure of lung function for assessing airflow limitation or asthma severity.

RV may be increased, as air has trouble escaping the lungs.

In asthma **FEV1:FVC ratio <80%**, may get as low as 20%, lower it is the worse the patient is,

aim is to get them back to at least 50%

Peak flow meters measure the peak expiratory flow (PEF), the fastest rate at which air can move through the airways during a forced expiration starting with fully inflated lungs.

The PEF correlates well with FEV1.

Peak flow meters are small, portable, convenient, and inexpensive.

Bronchial challenge:

In diagnosing asthma there should be some evidence of **bronchial hyper-responsiveness (BHR):**

>20% decrease in FEV1 in response to inhaled bronchoconstrictor (methacoline or histamine)

>20% increase in FEV1 in response to broncho-dilator.

The worse the BHR is the smaller the dose is for the % fall in FEV1.

Note- there is **no single** measurable abnormality that defines asthma

ACUTE PRESENTATION:

Acting Quickly

INITIAL MANAGEMENT OF ACUTE ASTHMA IN ADULTS

TREATMENT	MILD ATTACK	MODERATE ATTACK	SEVERE AND LIFE-THREATENING ATTACK
Hospital admission necessary	Probably not	Yes	Yes - consider ICU
Oxygen	High flow of at least 8 L/min to achieve an inspired oxygen concentration of about 50%. Monitor effect by oximetry. Frequent measurement of arterial blood gases in severe asthma and those not responding.		
Nebulised beta₂ agonist e.g. salbutamol or terbutaline, with 8 L/min O₂	5mg salbutamol in 2.5mL or 1mL 0.5% salbutamol + 3mL saline	Salbutamol 5mg x 2 or 2mL 0.5% + 2mL saline 1 - 4 hourly	<ul style="list-style-type: none"> • 2mL 0.5% salbutamol + 2mL saline nebulised every 15-30 mins • Give IV if no response to aerosol, e.g. salbutamol 250mcg IV bolus and then 5-10mcg/kg/hr.
Nebulised ipratropium bromide	Not necessary	Optional	1mL 0.05% (500mcg) ipratropium bromide with salbutamol 2 hourly
Oral corticosteroids e.g. prednisolone	Yes (consider)	Yes 0.5 - 1.0mg/kg initially	Give IV steroids initially; oral later
Intravenous steroids e.g. hydrocortisone (or equivalent)	Not necessary	250mg stat, where oral not convenient	250mg 6 hourly for 24 hours, then review
Theophylline/ aminophylline	Uncertainty exists regarding the benefits of this drug in the presence of maximal doses of beta ₂ agonist. IV aminophylline 5mg/kg then 0.5mg/kg/hr IV is an alternative to IV salbutamol.		
Adrenaline	Not indicated	Not indicated	For anaphylaxis only, give adrenaline 0.5mL of 1:1,000 (0.5mg) solution IM. For respiratory arrest, give 5mL of 1:10,000 solution slowly IV.
Chest X-ray	Not necessary unless focal signs present	Not necessary unless focal signs present, or no improvement with therapy	Necessary if no response to initial therapy or suspect pneumothorax
Observations	Regular	Continuous	Continuous
Other investigations	Not required	May be required	Check for hypokalaemia and treat if present

THUS:

for MILD ATTACK:

- don't admit to hospital,
- give **oxygen 8L/min (watch oximetry)**
- give nebulised **bronchodilator**
- give oral corticosteroids 0.5 to 1.0 mg/kg.
- OBSERVE REGULARLY

for MODERATE ATTACK:

- Admit to hospital,
- give **oxygen 8L/min, (watch oximetry)**
- give nebulised **bronchodilators: both Salbutamol and Ipratropium Bromide**
- give oral corticosteroids 0.5 to 1.0 mg/kg;
- give IV steroids (250mg)
- **OBSERVE CONTINUOUSLY: rush to CXR if condition fails to improve**

For SEVERE ATTACK:

- Admit to hospital, consider ICU
- give **oxygen 8L/min, (watch oximetry)**
- give nebulised **bronchodilators: both Salbutamol and Ipratropium Bromide**
- **Intravenous bronchodilators IF NOT RESPONDING TO NEBULISER**
- give IV steroids (250mg), later switch to oral

ADRENALINE only if anaphylaxis or respiratory arrest

- **OBSERVE CONTINUOUSLY: rush to CXR if condition fails to improve**

As per PBL case:

- **OXYGEN:**
- with face mask, 8Lmin

- **Salbutamol** (bronchodilator)
- **6 puffs via a small volume spacer and face mask every 20mins.**

- **Ipratropium bromide** (bronchodilator)
- **4 puffs via a small volume spacer and face mask every 20 mins for 3 doses then every 4hrs.**

- **Prednisolone**
- **1mg/kg orally**

PROGRESS

Salbutamol reduced to hourly after 4hrs and to 4 hourly by 48 hours.
Commence Prednisolone (daily).

LONG-TERM MANAGEMENT

AFTER ATTACK:

- Discharge on **4 hourly Salbutamol** and **daily Prednisolone.**
- cease **Prednisolone after 3 days.**
cease **Salbutamol after 1 week.**
commence **inhaled corticosteroids (Fluticasone Propionate 200mcg/day). (← Preventor)**

counsell Parents:

- about avoiding passive smoke exposure,
 - dietary avoidance (increase omega –3 oils in diet),
 - potential for inhaled allergen avoidance.
- advise regarding potential ways of reducing risks of asthma and atopic disease in future siblings.

-**Main stay of management is avoidance of triggers** and medications

– if these fail then consider immunotherapy – inject tiny amounts of the allergen (progress from frequent injections to monthly) seems to down regulate the immune response: i.e patient becomes desensitised

The 6 Step Plan advocated by the National Asthma Campaign (NAC). The NAC states that the management aims in asthma are to:

1. **assess the severity** of the patient's asthma - by taking a good history of symptoms, hospital admissions, medication requirements etc
2. **Achieve patient's best lung function** - by giving medications to treat the underlying inflammation and the symptoms
3. **Maintain best lung function** - by taking a careful history of attacks to identify trigger factors and then giving advice on how to avoid these factors
4. **Maintain best lung function** - by optimising the medications to the correct doses of the appropriate medications to keep the patient well
5. **Develop an Action Plan** - this is a step wise approach for the patient to follow if he or she develops symptoms or has a decline in peak flow measurements which herald the onset of an exacerbation. Early intervention with increased doses of medication can abort troublesome exacerbations.
6. **Educate and review regularly** - it is important for the patient to understand as much as possible about asthma and how they can detect deterioration and increase their medications accordingly. Patient education is vital in giving the confidence to take a role in managing their disorder.

Disease Definition

- Asthma is a chronic inflammatory disorder of the airways that involves complex interactions among inflammatory cells, mediators, and the cells and tissues in the airways. The interactions result in airflow limitation from acute bronchoconstriction, swelling of the airway wall, increased mucus secretion, mucous oedema and airway remodeling. The inflammation also causes airway hyperresponsiveness. As a consequence, airflow is limited and exacerbations (or attacks) with coughing –tight and often non-productive, wheezing, chest tightness, and difficulty breathing occur. The airways become sensitive to stimuli such as allergens, chemical irritants, tobacco smoke, cold air, or exercise. The resulting airflow limitation is **reversible** (but not completely so in some patients), either spontaneously or with treatment. When asthma therapy is adequate, inflammation can be reduced over the long term, symptoms can usually be controlled, and most asthma-related problems prevented.

Epidemiology

- Asthma is both common, and increasing in frequency - particularly over the past 10 years.
- **Most common in Aust. and New Zealand than in any other population**
- **Environmental/life style factors are presumably responsible for increases.** Asthma leads to a loss in health care costs, lost productivity, and reduced participation in family life.
- **Prevalence is increasing**, most rapidly among children, especially where urbanization is taking place. This may be linked to factors including housing with reduced ventilation, exposure to indoor allergens (such as domestic dust mites in bedding, carpets, and stuffed furnishings, and animals with fur, especially cats), tobacco smoke, viral infections (RSV in childhood), air pollution (nitrogen oxides), and chemical irritants.
- This increase is potentially preventable, provided we can identify the risk factors, and develop effective strategies to reduce them.

Aetiology

- Approximately 20% of children will wheeze during the first year of life, especially during a **viral respiratory tract infection**.
- The majority of these wheezy infants do not have asthma, and cease wheezing during preschool age.
- Those who continue to wheeze into school age **almost certainly have genuine asthma**, usually in association with other clinical atopy. This group generally have frequent recurrences of wheeze, plus considerable morbidity from their wheeze (such as troublesome cough and breathlessness, wheeze needing medical consultations, asthma medications, and hospital visits.)
- A number of risk factors associated with infant wheeze and asthma have been identified. However, when considering these risk factors, the inherent difficulties in distinguishing genuine infant asthma from infants who wheeze, but do not have asthma must be recognized. Further, the important difference between factors that actually cause asthma ('inducers') and those that simply result in exacerbations of asthma - in those who already have the disease ('triggers') - must be noted. The major risk factors for infant wheeze and asthma include:

Atopy in the infant

Namely, an abnormal tendency to develop IgE antibodies to allergens. Atopy is dependent upon both genetic susceptibility and appropriate allergen exposure (timing & levels). Atopy can be detected by development of clinical atopy [atopic eczema, allergic rhinitis, or asthma] or by **positive allergen skin prick tests (or RAST tests)** to food (metabisulphite, MSG, aspirin) or airborne allergens. Atopy is the strongest identified risk factor for the development of asthma, with an odds ratio of approximately 10.

- **ASIDE: Atopic eczema:** affects around 10% of the population. It usually starts in the first year of life, often on the face or alternatively affecting all the skin of the body (erythroderma). It often localises then to the extensor surfaces of the limbs before settling in the flexures. Involvement of the cubital and popliteal fossae is particularly common, and this often continues into adulthood. At the other end of the spectrum, the eczema may be generalised, and continue to be so throughout early life, and sometimes into adulthood. The main characteristic of atopic eczema is itch, and this will differentiate it from other common skin conditions such as psoriasis. It is usually outgrown around puberty, but in some the eczema continues into adulthood. It is rare for it to continue after the age of 50. Factors exacerbating condition- allergy, infection. Contact with irritants, **stress**. **Treatment includes** avoiding exacerbating factors, topical corticosteroids, emollients such as oatmeal baths, antibacterial therapy, night sedation, immunosuppressives (refer to LT 3.02 by Penny).

Positive family history of asthma

Asthma in the off-spring is particularly likely if the mother has asthma. Whether this is due to maternal genomic imprinting, or simply an 'allergic' fetal environment is unclear.

Exposure to maternal smoking

The adverse effects of smoking are predominantly on the fetus, resulting in smaller lungs & narrower airway calibre, and a greater tendency to wheezing illnesses in infancy.

Male gender

The male predisposition is due to higher frequency of viral lower respiratory infections in males; a greater tendency to wheeze with viral infections (believed to be on the basis of relatively smaller airway calibre); and a greater tendency to develop atopy.

High levels of indoor aero-allergens

The major allergen in coastal regions of Australia is house dust mite (DerP1). In more arid regions the mould, *Alternaria*, is more relevant.

Low birth weight / preterm delivery

Infants born less than 2.5 kg or less than 37 weeks gestation are at greater risk of wheezing illnesses in infancy. Chronic lung disease of prematurity (or broncho-pulmonary dysplasia), represents the extreme example of this risk factor.

Poor air quality/air pollution

There is conflicting literature on the role of indoor & outdoor air quality on asthma (including PM10/particulates, ozone, SO₂, & NO₂). The current consensus is that while these agents may act as triggers of attacks, they do not cause asthma.

Viral infection

Respiratory viruses can trigger bouts of wheeze in normal infants, especially RSV, which causes annual winter epidemics of acute viral bronchiolitis. Those with anatomically small airways are likely to have increased wheeze during viral lower respiratory infections. Respiratory viruses are also the most common identifiable trigger of acute asthma in infants & young children with pre-existing asthma.

Small (or excessively 'floppy') airways

Infants born with relatively small calibre, or soft, collapsible airways, can be identified in the newborn period by measuring abnormally low flow rates on pulmonary function testing. Such infants are likely to suffer wheezing illnesses during infancy and have a favourable natural history with subsequent lung/airway growth. Epidemiology studies indicate this is the cause of approximately 50% of infant wheezing. With the exception of maternal smoking, an obvious problem with many of these risk factors is our current inability to remove or reduce them.

Other factors appear to decrease the likelihood of asthma. These include: frequent infections in early infancy; a diet that regularly contains fish (especially oily fish); being born overseas, breast fed infants have fewer allergies; and belonging to indigenous populations.

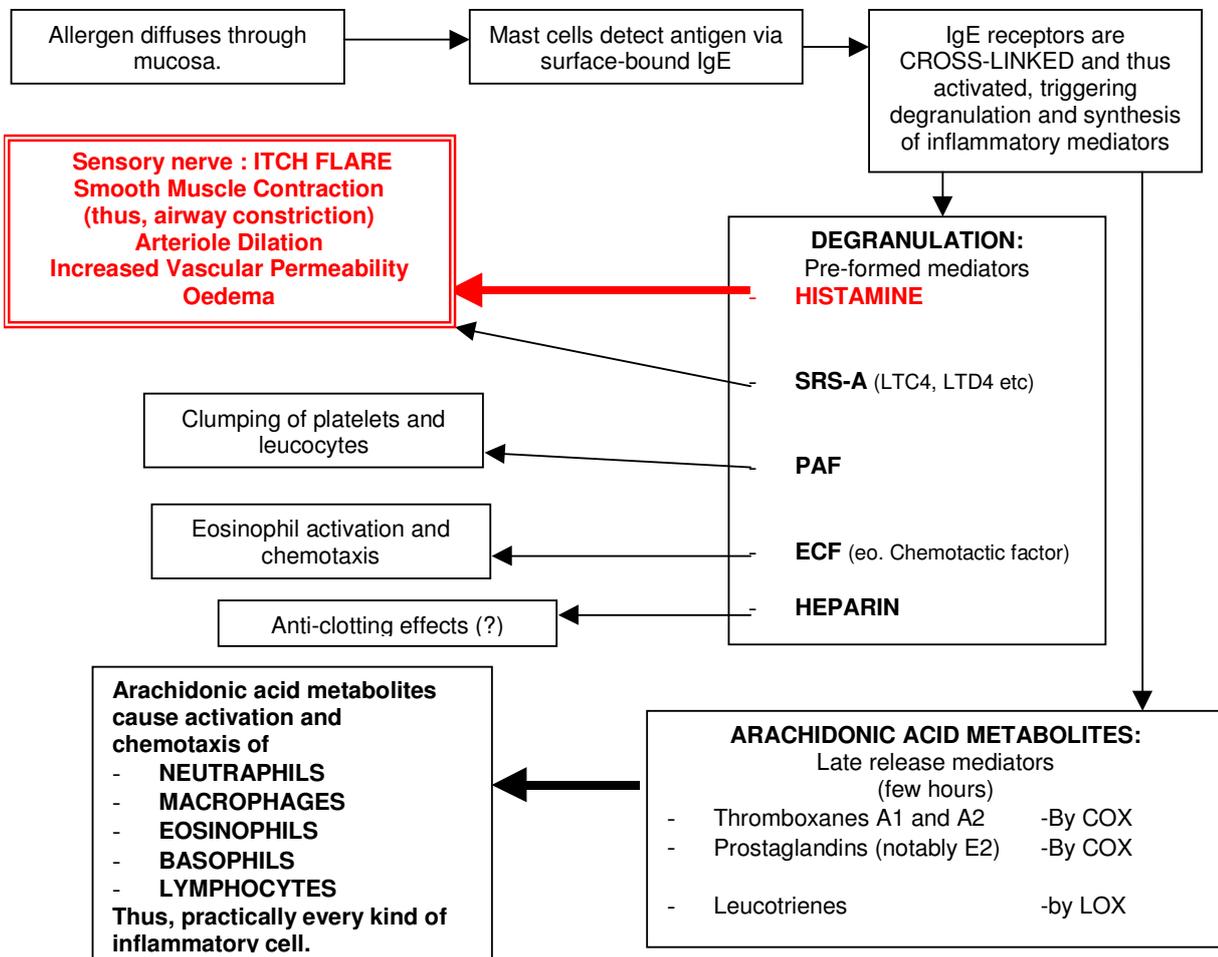
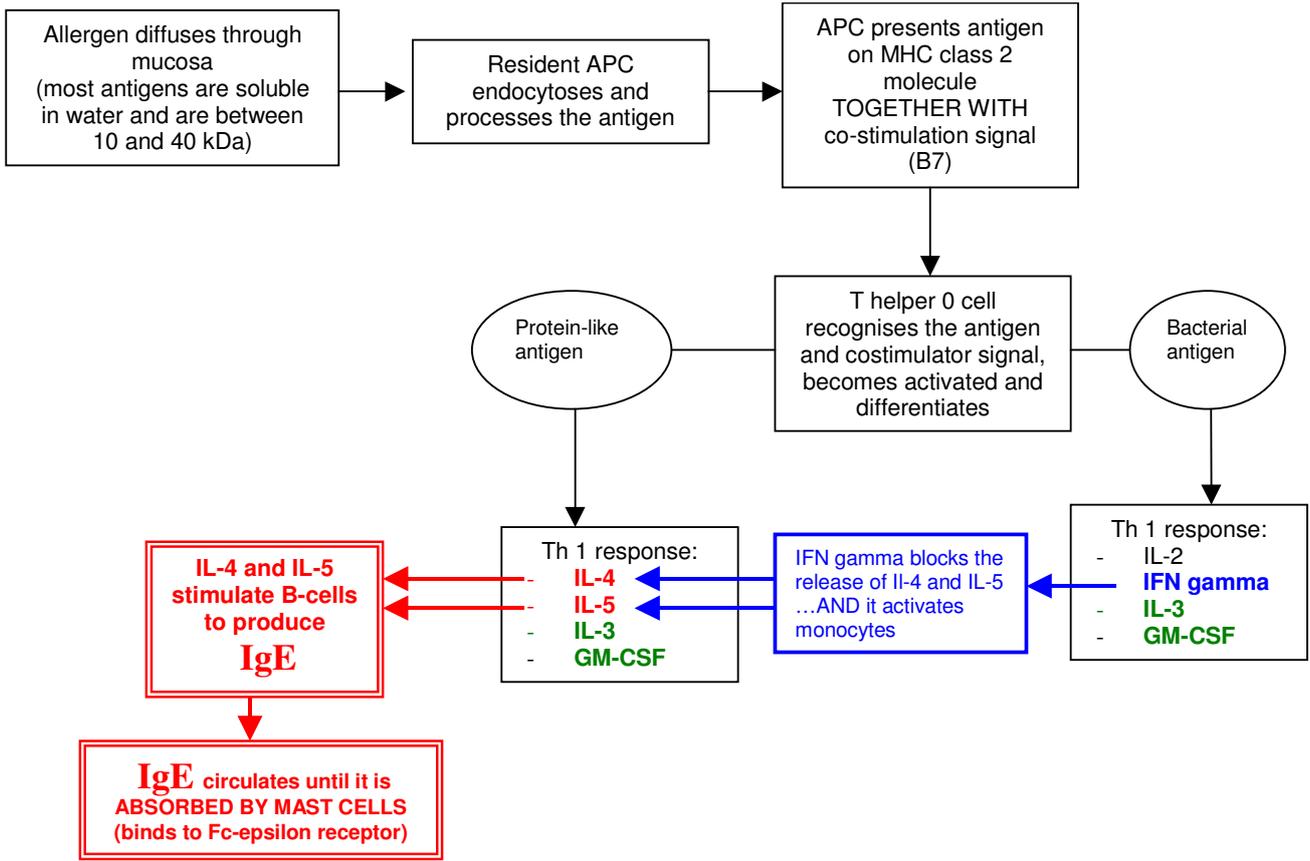
Prognosis

The prognosis of asthma remains good with as many as 60%-80% of those who have the disease being able to lead normal lives without any significant disruptions.

But **between 10%-20% of patients continue to have severe attacks throughout their lives.** Fortunately asthma is not a progressive disease. The mortality rate among asthma patients is low though it has been on the rise of late.

PATHOGENESIS:

Mechanism 3.02



Pathophysiology of wheezing

Wheezes = high pitched (~400Hz) continuous sounds superimposed on the normal breath sounds; the sound is continuous over 0.25 to 1.5 seconds of breathing

- as opposed to "crackles" which are a series of discontinuous "popping" sounds
- ... Referred to as "adventitious" sounds.

Wheezing is produced in the trachea or major bronchi:

Air velocity is too low in the lesser airways

The mechanism of this has been compared to the production of sounds by wind-instruments which use a vibrating reed to produce their sound (eg a clarinet)- this occurs when the airway lumen is narrowed to the point where the opposite walls are almost in contact.

The acceleration of gas flow through the narrowed airway induces an oscillation of the airway walls.

THUS: wheezing depends on degree of constriction and degree of airway "floppiness"

THERE IS NO CORRELATION between intensity/pitch of wheezing and pulmonary function.

INSPIRATORY wheezes (stridor) are a sign of more severe obstruction- usually heard better at the neck rather than chest.

In auscultating, note

- pitch
- intensity
- location
- duration in the respiratory cycle (short or long)
- relationship to the phase of respiration (inspiratory or expiratory)

DYNAMIC narrowing of airways occurs at the point in expiration where the pressure inside the lumen is less than the pressure outside (thus, the airway buckles under outside pressure)

equal pressure point theory - When a person takes a full breath in and then forcibly exhales there is a limit to the maximal flow that will be achieved at each lung volume. Near TLC the flow will be high and flow will decrease as lung volume is exhaled. Once enough effort is expended to reach flow limitation, any further effort will not lead to increased flow. One theory which helps to explain this phenomenon is called the **EQUAL PRESSURE POINT (EPP) THEORY**. The key elements involved include the pleural pressure or pressure outside the airways (Ppl) which is usually negative during relaxed expiration, tending to keep the lungs inflated, and the elastic recoil pressure of the lung tissue (Pst[L]) which tends to empty the lungs. The tissue forces driving relaxed expiration are the sum of these two values. If airflow resistance increases, these driving forces may be insufficient to produce airflow and expiration must become an active process; now Ppl becomes positive during expiration and the pressure within the alveoli increases. This pressure will progressively fall along the airways (referred to as "downstream") to reach a pressure of zero at the mouth. Downstream from the point where Ppl exceeds the intraluminal pressure, dynamic compression of the airways can occur, and wheeze is produced as a result of the dynamic narrowing of these larger airways.

No theory explaining inspiratory wheezes has yet been proposed

MECHANISMS OF SHORTNESS OF BREATH

Humans can perceive several respiratory sensations:

- localised irritation,
- respiratory discomfort,
- perception of position and motion.

"Breathlessness" is rated differently by individuals. Investigators have also assessed respiratory sensations in different ways making comparisons between studies difficult
THUS: one must be as precise as possible with the use of language, both in defining the experimental task to the subject and interpreting the results.

Assessment of breathlessness

- Indirect methods,
 - **clinical interview,**
 - **questionnaires for assessing exercise limitation**
 - **exercise tolerance.**
- Direct methods,
 - scaling of respiratory mechanical events,
 - scaling of breathlessness ratio, linear scaling by visual analog, etc.

Mechanisms of breathlessness

The neurophysiological mechanisms are poorly understood.

Exercise results in many simultaneous physiological changes which could be sensed.

In disease, pathological changes may cause earlier activation of the same mechanisms or additional "abnormal" afferent neural activity.

- **CHEMICAL STIMULI:** (hypercapnia, hypoxia, and acidosis). Triggered by low oxygen or high carbon dioxide in bloodstream.
- **PULMONARY RECEPTORS:** (stretch, irritant, C-fibres) contribute VERY LITTLE to the sensation of breathlessness
- **RESPIRATORY MUSCLES:** (perception of force/pressure, load, volume). THEORY: **tension developed in the respiratory muscles can be sensed as inappropriate relative to the demand for ventilation. HOWEVER:** paralysis studies suggest the role of these mechanoreceptors is not essential for sensation of SOB.
- **CENTRAL RESPIRATORY COMMAND: MOST IMPORTANT COMPONENT.**
Awareness of motor output to the respiratory muscles (via collateral discharge within the CNS) **rather than afferent feedback from the muscles.**

Behavioural Sciences

- **The chronically or recurrently ill child** –intra personal issues
 - regressive behaviour.
 - low self-esteem,
 - oversensitivity.,
 - anxiety disorder.,
 - moodiness and depression,
 - denial/rebellion,
 - secondary gain (favoritism in the family).
- **Family issues** – **authoritative parenting** as most beneficial
 - neglecting, authoritarian or indulgent styles can be problematic
 - **Parental compliance** (giving medications to sick child) **ranges between 11 and 89%**

Physiology

Lung elastic recoil- decreases w/age, no known effects of height/race, no effects of gender in –vivo, diff. found in resp. tests likely related to greater resp. muscle strength in men

Lung volumes- depends on distending pressure of lung volume. Height is best predictor of lung volume (taller =larger lung volume), however, size of alveoli same in lungs of differing sizes.

-**females have smaller lungs for height; however, the alveoli size is the same in both genders.**

-for a given height, there is a smaller lung volume in colored races (Indians having the smallest lung volumes among the races).

- $C_1 \times V_1 = C_2 \times (V_1 + V_2)$

Respiratory Equations

Diffusion = $V_{gas} = \frac{A}{T} D(P_1 - P_2)$ WHERE: A=area. T=thickness P=pressure D-type of material MW-molecular weight. $D \sim \frac{Sol}{\sqrt{MW}}$

- $\frac{1}{Dl} = \frac{1}{Dm} + \frac{1}{\sigma Vc}$

Microbiology

Acute asthma in kids is often the result of upper airway virus.

Major viruses responsible for precipitating exacerbations of asthma are **rhinoviruses and respiratory syncytial virus (RSV)**

- RSV infects over 95% of children by the end of their second winter.
- **About 40% of these children develop bronchiolitis**, an acute lower respiratory infection characterised by tachypnoea, hyperinflation and crackles.
- Babies who develop bronchiolitis severe enough to require hospitalisation have a **high risk (around 50%) of developing asthma.**

- RSV-specific IgE has been found attached to nasopharyngeal cells in infants with RSV and wheezing.

Other viruses less commonly implicated are parainfluenza viruses, enteroviruses and adenoviruses.

In school age children, rhinoviruses are the commonest viral precipitant of asthma attacks. Rhinoviruses use ICAM-1, an intercellular adhesion molecule, as a cell receptor for attachment and entry.

They also stimulate IL-8 production; thus causing inflammation and contributing to wheeze-generating airway narrowing

Although other organisms such as *Mycoplasma pneumoniae* in school aged children, *Chlamydia trachomatis* in infancy, and *Chlamydia pneumoniae* may also cause wheezing, these are in fact extremely rare causes of acute exacerbations of asthma in prospective studies. **Bacteria do not cause wheezing**, and antibiotics are not routinely prescribed for acute asthma

IN SUMMARY:

Normal child responding to viral infection responds with TH1 cells, IFN gamma and IL-2.

Atopic child responds with TH2 cells, thus IL-4, IL-5 and subsequently GM-CSF-eosinophilic infiltration of the airways (and not the cytokines produced by TH1) and collectively which results in the observable granulocyte and monocyte infiltration.

Hygiene Hypothesis –kids brought up in a more sterile environment are **more likely to develop asthma**

Immunology of HYPERSENSITIVITY

Allergic reactions divided into four main types (Gell and Coombs Types I-IV).

Type 1 – IgE mediated (urticaris)

Type 2 – antibody mediated (auto-immune) pemphigus

Type 3- immune complex (allergic vasculitis)

Type 4 – delayed hypersensitivity (allergic contact dermatitis)

On a clinical basis, reactions can be classified according to the time of onset of symptoms. Symptoms occurring within minutes of an immune reaction, it is called an immediate or early reaction. Symptoms starting after hours, is a late reaction, and after days, it is delayed reaction. The responses to antigens do not usually involve only one type of hypersensitivity reaction, and the immune response is best considered as a sequence of events involving interactions between many cell types, antibodies and complement.

The Type I immediate reaction is caused by IgE (and possibly IgG). Antigens which cause Type I reactions are called allergens. When the allergen reacts with IgE attached to the surface of the mast cell, the cell degranulates and releases chemical mediators (histamine, SRS-A, ECF, PAF) responsible for the symptoms. Type 1 reactions depend on the presence of specific IgE on high affinity receptors on mast cells. There are also IgE receptors of both low and high affinity on other cell types, including eosinophils and macrophages.

The mechanisms responsible for the triggering and maintenance of allergic disorders: IgE synthesis results from the collaboration between a subset of T helper (Th) cells which produce IL-4, but not IFN-gamma (Th2 cells). The Th2 cells, because of their ability to produce IL-5 as well as IL-4, are also responsible for the eosinophils often associated with hyperproduction of IgE in allergic subjects. In contrast, T helper cells which do not produce IL-4 (Th1 cells), or which produce high concentrations of IFN-gamma, do not support IgE synthesis; in fact, the IFN-gamma can suppress IL-4-dependent IgE synthesis.

The reasons for promotion of a prevalent Th2 response to environmental allergens (such as foods, HDM, animal dander, pollen etc) in atopic subjects are unknown, but almost certainly involve a genetic predisposition as well as environmental influences.

Atopic diseases (diseases in which atopy is a common although not universal finding) include atopic dermatitis, immediate food hypersensitivity, asthma and allergic rhinitis. An interesting pattern is seen in the development of atopic disease in childhood with atopic dermatitis and immediate food hypersensitivity being prominent in infancy and asthma and allergic rhinitis becoming more prominent in the pre-school and school years. This corresponds to the pattern of allergen sensitisation with early and often transient responses to ingested allergens and a progressive increase of inhalant allergen sensitisation with increasing age. Evidence of IgE sensitisation to allergens can be demonstrated by either skin prick tests or blood tests (RAST - radioallergosorbent test).

ATOPY

NB eczema = dermatitis; atopic eczema = endogenous eczema

Epidemiology: 5% of population but occurs at some stage in childhood in 10-15% of kids

Prognosis: majority of children with early-onset atopic eczema will spontaneously improve and clear before the teenage years, 50% clear by age of 6; a few will get recurrence as adults; if onset is in late childhood or in adulthood chronic/relapsing course

Clinical features: itchy erythematous scaly patches esp. in flexures eg elbows, ankles, behind knees and around neck; in infants starts on face before spreading to body; very acute lesions may weep or exude and can show small vesicles; scratching can produce excoriations (superficial loss of substance) and repeated rubbing produces skin thickening (lichenification) with exaggerated skin markings; in patients with pigmented skin eczema often shows reverse pattern of extensor involvement and it may be papular or follicular in nature and lichenification is common, also post-inflammatory hyper or hypopigmentation may occur which is often slow to fade after control of eczema outbreak.

Associated features: involvement of nail bed may produce pitting and ridging of nails; skin of upper arms and thighs may feel roughened due to follicular hyperkeratosis (keratosis pilaris); palms may show very prominent skin creases (hyperlinear palms); dry, fish-like scaling of skin on lower legs (ichthyosis vulgaris)

Exacerbating factors: strong detergents, chemicals, woollen clothes, infection (of skin or systemic), teething in young kids, anxiety/stress, cat and dog fur, house dust mite?, food allergens (eg dairy in infants under 12 months old)

Complications: broken skin frequently becomes secondarily infected by *Staphylococcus aureus* or in neck and groin *Streptococci sp.* can colonize eczema; clinical signs of such infection are crusted, weeping, impetigo-like lesions; cutaneous viral infections (eg viral warts, molluscum) are often widespread in atopic eczema usually caused by scratching – such infections can occasionally be very severe or even fatal; signs of such viral infection are multiple small blisters or punched-out crusted lesions associated with malaise and pyrexia and needs treatment by oral aciclovir or IV aciclovir if severe; conjunctival irritation and less commonly keratoconjunctivitis and cataract can occur; retarded growth in children with chronic, severe eczema

Investigations: diagnosis is clinical; radio-immunoabsorbent assay of blood will show high serum IgE levels and possibly peripheral blood eosinophilia

Treatment:

GENERAL

- avoid irritants (eg soaps, cats),
- wear cotton clothes,
- avoid overheating/overdressing,
- diet controls (eg dairy-free for those under 12 months old with known allergy, under medical supervision and with appropriate supplements)

TOPICAL –

- topical steroid* twice daily when needed
- + emollient frequently (eg. oat soap)
- + bath oil and soap substitute (eg aqueous cream)

* **NB steroids used on face should be MILD (<2.5% hydrocortisone);**

steroids used on body should be no greater than <.025% bethamethasone valerate in adults but young children should only use MILD steroids;

- in severe outbreaks, potent steroids (<.1% bethamethasone valerate) may be used for **no more than 10 days in adults only;**
- treatment of palms and soles (not dorsal surfaces) may require more potent steroids as the skin is thicker;
- regular use of emollients may lessen need for steroids;
- only use steroids on inflamed skin;
- use sufficient to leave a glistening surface on skin;
- use weaker steroids in flexures (eg groin, under breasts) as apposition of the skin at these sites occludes the treatment and increases absorption

EDUCATION and EXPLANATION to patient

ADJUNCT THERAPIES –

- sedating antihistamines,
- occlusive bandaging (to prevent scratching),
- oral antibiotics and/or antiseptic baths for bacterial infection

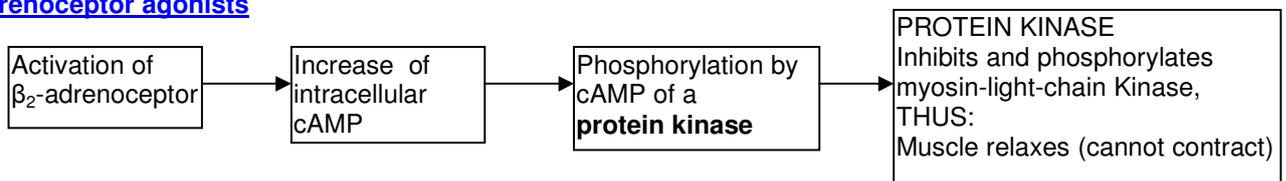
MORE AGGRESSIVE TREATMENTS –

- ultraviolet phototherapy,
- **cyclosporin**
(selective immunosuppressant that inhibits IL-2 secretion by T lymphocytes – beware renal damage and hypertension),
- **azathioprine** (immunosuppressant)

Pharmacology of BRONCHODILATORS and CORTICOSTEROIDS

Bronchodilators:

β_2 -adrenoceptor agonists



These drugs are physiological antagonists that dilate the bronchi by direct action on the β_2 -adrenoceptors on the smooth muscle causing relaxation of the bronchial muscle. The relaxation of the muscles occurs by increasing intracellular cAMP, which activates a protein kinase inhibiting muscle contraction by phosphorylating and inhibiting myosin-light chain kinase. They also inhibit mediator release from mast cells, the release of TNF α by monocytes and they may increase mucus clearance by action on cilia. They are used to treat asthma and chronic obstructive lung disease.

β_2 -adrenoceptor agonists are usually given by inhalation of metered dose of aerosol, powder or nebulised solution although they can be given by injection or orally.

Types of β_2 -adrenoceptor agonists are used in asthma:

- (a) **Short acting (salbutamol and terbutaline)**- inhaled drugs where the maximum effect is in 30 mins with a duration of 4-6 hrs; consequently they are used as needed to control symptoms.
- (b) **Longer acting (salmeterol)** – inhaled drug with a duration of 12 hrs so are given on a regular basis as adjunctive therapy for patients whose asthma is not controlled by glucocorticoids
- (c) **Ipratropium – inhaled muscarinic antagonist** and moderately effective bronchodilator reduces reflex vagal bronchoconstriction from histamine stimulation of sensory receptors in the airways.
- (d) **Rimiterol** (shorter duration than salbutamol), pibuterol, retrotelol and bambuterol (prodrug of terbutaline) are now available.

Adverse effects of β_2 -adrenoceptor agonists include tremor, β_2 -agonist tolerance (reduced by steroids, nervous tension and tachycardia).

Nonselective β_2 -adrenoceptor agonists (adrenaline and isoprenaline) which act on both β_1 and β_2 receptors are no longer used. β_2 -adrenoceptor antagonists (propranolol) annul the effect of compensatory endogenous adrenaline and can cause wheezing in asthmatics and precipitate a serious attack.

Xanthine drugs

These are pharmacologically active naturally occurring methylxanthines- theophylline (1,3 dimethylxanthine or aminophylline used medically), theobromine (in cocoa) and caffeine.

Xanthines are bronchodilators but do not prevent bronchial hyper-responsiveness. They can cause increased alertness, tremor, nervousness, gastrointestinal problems (nausea, vomiting and anorexia), interfere with sleep, stimulate respiration and the heart, cause vasodilation (some cause vasoconstriction of cerebral blood vessels) and have a weak diuretic effect involving increased glomerular filtration rate and reduced tubal reabsorption.

The way in which these drugs produce effects in asthma are unclear. Theophylline inhibits phosphodiesterase (PDE) and increases cellular cAMP levels which causes muscle relaxation.

Xanthine drugs are given orally in sustained release preparations or by slow IV injection of a loading dose followed by IV infusion for treatment of status asthmaticus. Theophylline is well absorbed by the GIT and metabolized by the liver and has a plasma half life of about 8 hrs. The half life is prolonged in liver disease, cardiac failure, viral infections and decreased in heavy cigarette smoking and drinking. Theophylline plasma concentration is decreased by drugs that increase P450 enzymes (rifampicin, phenobarbital, phenytoin, carbamazepine) and its serum concentration is increased by drugs that inhibit P450 enzymes (Oral contraceptives, erythromycin, ciprofloxacin, calcium channel blockers, fluconazole and cimetidine).

Theophylline is used as a second line drug in asthma (in addition to or as an alternative to steroids and other anti-asthmatic agents in patients not responding to β_2 -adrenoceptor agonists. It is also used to reduce symptoms in chronic obstructive pulmonary disease.

Histamine H₁ receptor antagonists (Antihistamines)

Histamine H₁ receptor antagonists are not used for therapy even though mast cell mediators play a role in the immediate phase of allergic and exercise induced asthma.

The antihistamines are used to treat allergic conditions such as hayfever, insect bites and stings, urticaria, drug sensitivity reactions and pruritis. Some **non-sedating antihistamines (because they don't cross the blood brain barrier)** ie loratidine have been effective in clinical trials in mild atopic asthma.

Muscarinic receptor antagonists

These drugs are often called parasympatholytic because they selectively block the effects of the parasympathetic nerve activity. They are competitive antagonists with a chemical structure containing an ester and basic groups in the same relationship as acetylcholine but they have an aromatic group instead of the acetyl group. Atropine and hyoscine are alkaloids(tertiary ammonium compounds) found in plants and are lipid soluble so can pass the blood-brain barrier.

Ipratropium is used as an inhaled antiasthmatic, with a max effect after 30 mins lasting 3-5 hrs, it relaxes bronchial constriction caused by parasympathetic stimulation especially in allergic and irritant asthma. Ipratropium is a quaternary derivative of N-isopropylatropine and it does not discriminate between muscarinic receptor subtypes. It may block M₂autoreceptors on cholinergic nerves increasing acetylcholine release and reducing the effectiveness of its antagonism at the M₃ receptors on smooth muscle. It is not effective against allergen challenge but inhibits the augmentation of mucus secretion in asthma and may increase mucociliary clearance of bronchial secretions. It has no effects on the late inflammatory phase of asthma.

Anti-inflammatory agents:

Glucocorticoids

Glucocorticoids are used in management of chronic asthma rather than in acute.

- **decrease the formation of cytokines**, particularly Th2 which recruit and activate eosinophils and promote production of IgE and the expression of IgE receptors.
- **inhibit the generation of the vasodilators** PGE₂ and PGI₂ by inhibiting induction of cyclooxygenase 2.
- **inhibit production of spasmogens** LTC₄ and LTD₄ -Because they also induce lipocortin
- **decrease synthesis of LTB₄ and PAF** (leukocyte chemotaxins) reducing recruitment and activation of inflammatory cells.
- **inhibit the allergen induced influx of eosinophils** into the lung
- **upregulate β_2 -adrenoceptors**,
- **decrease microvascular permeability**
- **reduce mediator release from eosinophils.**

The reduction in production of IL3 (regulates mast cell production) may explain why long term steroid treatment reduces the early phase response to allergens and prevents exercise induced asthma.

The main drugs used are beclomethasone, budesonide and fluticasone given by a metered dose inhalation with the full effect occurring several days after commencement of therapy. In chronic or severe and rapidly deteriorating asthma a short course of a reduced dose of oral glucocorticoid (prednisolone) combined with the inhaled steroid is used. In status asthmaticus hydrocortisone is given IV followed by oral prednisolone.

Side effects include oropharyngeal candidiasis (thrush), dysphonia (voice problems) from using inhaled steroids but these can be reduced by using a spacer. Other side effects include adrenal suppression.