Lecture 1: Clinical Introduction to the Respiratory System

Respiratory diseases can be classed into four broad categories: infections, airway diseases, small lung and pulmonary vascular.

Airway diseases may include; obstructive sleep apnoea (often extra weight around the neck, such as in obesity, will cause the airway to collapse at night), bronchial carcinoma (for which clubbing of the nails may be a clinical sign), asthma, COPD and cystic fibrosis.

We use spirometry to distinguish between normal and obstructive airways along with restrictive conditions (such as small lungs):

**Normal:** Normal FEV₁ and FVC.

**Obstructive airways:** reduced FEV₁ and FVC normal or low. Usually with a FEV₁/FVC of less than 70%.

**Restrictive conditions:** FEV₁ and FVC both reduced. FEV₁/FVC ratio of above 70%.

Note stridor is respiratory wheeze and is pathological.

Small lung diseases include: interstitial lung diseases, pleural diseases (tumour, effusion), obesity, chest wall/muscle disease.

When we describe a condition of the lung we need to specify the location in terms of lobes, unilateral or bilateral etc. We may also classify the pneumonia on whether is is community acquired, hospital acquired or through aspiration. A multilobe pneumonia is high risk. We may also do microbiological testing to help define the nature of the infection.

The complications from pneumonia include: effusion, empyema (thick, separted plus in the pleura) and abscess. A patient with an abscess is likely to loose weight and be critically ill- treatment of such an abscess required 6 weeks of antibiotics and nutritional support. To treat pneumonia, we give oxygen, fluids, pain relief, antibiotics and monitor the patient over time.

**Pleural effusion:** fluid collection around the lining of the lung. The causes include:

- Infection
- Malignancy
- Pulmonary embolus
- Heart failure (bilateral effusions seen here)
- Trauma (a blood effusion seen here)

The first three are the major causes of unilateral pleural effusion.
Histologically we see: submucosa widened by smooth muscle hypertrophy, oedema, and inflammation (mainly eosinophils). The lumen has inflammatory markers. Smooth muscle is widened and there is oedema.

Cough at night: think asthma. We cannot diagnose asthma until the child is past 2 years of age due to the development of the respiratory system.

Note with recurrent infections we should consider cystic fibrosis but these tend to be lower respiratory tract infections and we now screen in infancy for CF so it is unlikely in this case.

**Case 4 Mr Pawar**

History: 65y old male, smoker. Frequent chest infections & Chronic productive cough. Presents with worsening shortness of breath. Examination: RR 12, O2 sats 89%. Chest: transmitted sounds

**COPD**

Defined as persistent productive cough for ≥3 months over ≥2 years. Worldwide, affects ~5% population. Most cases associated with smoking.

There are black carbon deposits in lung with an inflammatory response in lungs. There is inflammation & narrowing of small airways (bronchitis). Histologically we see increased chronic inflammatory cells in submucosa (neutrophils & macrophages) and breakdown of lung tissue (emphysema). There is loss of alveolar walls and the damage is cumulative and permanent. The chronic inflammatory cells are in the lung [here we are macrophages] and the loss of the alveolar walls decreases the ability to breathe. These patients are at high risk of bullae – where the alveoli come together. Also bare in mind if we ventilate these patients there is risk of inducing a pneumothorax.

**Case 5 – Mr Gibbins**

History: 67y old male, smoker. Presents with losing weight and feels tired all the time. Chronic cough, now noticed blood in tissue when he coughs. Examination: appears thin. Chest examination reduced breath sounds on right.

**Lung Cancer**

Lung cancers are carcinomas, arise from epithelial cells. Histologically we see nests of polygonal cells with pink cytoplasm, distinct cell borders. There are Two broad classes: non-small-cell lung carcinoma & small-cell lung carcinoma which is important for management and predicting outcome. The tumor is often highly vascularized and the alveoli are filled with cells. There is mixing of the cell bodies.

CXR looking for: Mass, widening of the mediastinum, atelectasis (collapse of the lung. Note this ay pull up the diaphragm, consolidation and pleural effusion (note the blunting of the costophrenic angle would tell us this).
Lecture 5: **Ventilation and Airway Resistance**

The pleural cavity is filled with fluid which acts like water between two sheets of glass; it has hard to separate but allows for movement over one another. This creates a negative pressure below that of the atmosphere. Both the chest wall and lungs have elasticity; the chest wants to expand outwards whilst the lungs wish to recoil. There is a balance, therefore, between the two. When they are exactly balance we are at functional residual capacity.

When we breathe in we stretch the lung; muscles work to do this. This increases the volume of the lung which in turn leads to a fall in pressure (as the gas is now spread out in a wider volume). The pressure falls roughly 1-2 mmHg below that of the atmosphere so air moves in. Pressure then is stabilized. So when we stop breathing in there is a reduction in volume of the lungs as the lungs recoil, the pressure rises to above that of the atmosphere and so air leaves the lungs.

**Boyle's law** states that pressure x volume equals a constant: \( P \times V = K \). This states that for any given quantity of gas in a container the pressure is inversely related to the volume of the container. So the driving force of air movement is the difference between atmospheric and alveolar pressure. Thus pressure changes determine direction of flow.

During inspiration the diaphragm flattens and moves down. This pushes the ribs out slightly and crushes the abdomen which also helps bring the ribs out. About 2/3 of gas exchange is facilitated by the 1-1.5cm movement of the diaphragm. External intercostals also contract moving the ribs up and out. The contraction pulls the ribs up as they are arranged anteriorly inferiorly. Note breathing is not an autonomic process. The phrenic nerve (C3,4,5) controls the diaphragm and spinal nerves T1-T11 control the external intercostals. The movement of muscles causes an increase in the volume of the thoracic cavity. The external intercostals do the other 1/3 of gas acquisition.

During quiet normal breathing expiration is passive. The chest wall and lungs recoil which decreases the volume of the lungs causing an increase in alveolar pressure so air leaves the lung. Forceful expiration is driven by contraction of expiratory muscles which cause a greater, more rapid decrease in lung volume. Such as in exercise.

At functional residual capacity the recoil of the lungs and the recoil of the chest wall are in balance. A pneumothorax can cause the lung to collapse. A CXR can show a mediastinum shift too.

The work of breathing is composed of airway resistance (30%), compliance (65%) [this is the elasticity of the lung] and frictional resistance. At rest the work of breathing uses around 5% of our oxygen consumption, this may increase up to 30% during exercise.

The major sites of airway resistance are the upper airways and the medium sized bronchi. This is because the cross sectional area increases as you move down the lung and as such resistance falls. Since flow = change in pressure divided by resistance \((Q = \Delta P/R)\); if we increase resistance then the flow will fall.
steeper part of the compliance curve so more gas goes to the bottom of the lung than the top. We can measure this with radiolabelled xenon.

Compliance will depend on the elasticity of the lungs and the surface tension of fluid lining the alveoli.

Lungs are elastic due to elastic fibers in the connective tissue. Forces exerted by these fibers generally oppose lung expansion because as the lung stretches the fibers tend to recoil. Collagen gives rigidity to the lungs.

Surface tension of lungs is caused by the air-liquid interface formed by the thin layer of fluid lining the surface of alveoli. The law of laplace states that the air pressure (P) within a spherical alveolus is directly proportional to the surface tension (T) and inversely proportional the alveolus radius:

\[ P = \frac{T}{r} \]

P is the air pressure inside relative to outside. As a consequence of this if large and small alveoli had the same surface tension, small ones would not fill but would collapse into larger ones. Basically gas would shift from small to large alveoli and thus would not fill. This is if they are all at the same tension.

Surfactant is a phospholipid produce by type 2 pneumocytes that helps to decrease surface tension and so increase lung compliance and thus reduce breathing work. Being born premature is associated with respiratory distress syndrome as surfactant isn’t made yet. This acts to equalize the pressure, if surface tension is reduced. In smaller alveoli there is a higher concentration of surfactant in comparison to surface area so tension is reduced. So surfactant concentration is proportional to alveolar size; and its ability to reduce tension is linked to this as well.
• 1 or 2 – Increased risk of death (1-10% mortality risk)
  Hospital Referral Considered
• 0 – Low risk of death (< 1% mortality risk)
  Do not usually require hospitalisation

CAP tends to be caused by S. pneumonia [1/3 caused by this: classically follows an acute viral infection], H. influenzae [can cause bronchitis] and viruses. S. aeurues may also be a cause and again this is common post a viral infection.

In the hospital setting the pathogens tend to vary. In intensive care we see S. pneumoniae, Legionella species and viruses again. Legionella species tend to cause hyperneutrima, fever and respiratory failure. Atypical pathogens in the community can cause hospitalization even though these are rare in the community.

Steptococcus pneumonia

A gram + diplococcus. It is lanceolate (elongated). >90 capsular serogroup, the capsule is pathogenic. The bacteria can escape macrophage engulfment. Diagnosed by microscopy and culture or by antigen detection- use urine or other sterile fluids for this. Causes lobar pneumonia and bronchopneumonia. Complications include empyema and meningitis. It is alpha haemolytic on blood plates which means it destroys RBC leaving a green color. C. B haemolytic organisms will completely clear the plate. More common in older age as a disease. Penicillin resistance increasing, although rare in UK [but may be imported from high risk areas e.g. Spain is seeing a rise in resistance]. Significant cause of mortality amongst susceptible individuals e.g. elderly, renal failure, splenectomy. The spleen is key in fighting capsulated organisms and so these patients may require prophylactic antibiotics and should be vaccinated. Vaccine available against 23 serogroups and covers 95% of invasive disease

Haemophilus influenzae

Gram negative bacillus that is capsulated (a-f) types as well as unencapsulated strains. Diagnosed by culture and requires haemin and NAD (nicotinamide adenine dinucleotide) for growth. Causes a LRTI/pneumonia in adults which is more common in chronic lung disease and smokers. Complications include Meningitis and epiglottitis in (serotype b = Hib). 20% are β-lactamase positive [give amoxiclav if resistant]. HiB in particular can cause systemic disease in children; there is now a vaccine available. Additionally, splenectomy patients are at increased risk due to the capsule.

Atypical Pneumonias

Pneumonia caused by atypical pathogens. Usually, but not always, insidious onset (chronic).
Classically, patients have a non-productive cough, fever, headache, and a chest radiograph more abnormal than expected from clinical assessment- tend to see fluffy shadowing on both lungs which wouldn’t be expected from listening to the lungs alone. Infection may be sub-clinical and resemble a non-specific viral infection. Many cases probably go undiagnosed.

To treat pleural effusion and lung abscess we need to drain the pus and give antibiotics for 2-4 weeks.

**Key Points**

- LRTI is a common illness in both primary and secondary care
- LRTI can be sub-divided; with different aetiologies, outcomes and management
- Acute exacerbations in COPD and pneumonia are common
- Severity of illness can be assessed, which determines management (CURB65, CRB65, COPD)
- There are differences between community- and hospital-acquired infection.
Asthma has a complex relationship between the allergy response, airway hyper-responsiveness, inflammation and respiratory infections. These all act to cause smooth muscle contraction, mucus secretion and an increase in blood vessel permeability leading to the symptoms seen.

Thus this provides us with targets. For infections we can use antibiotics, inflammation we use anti-inflammatory, use bronchodilators for the smooth muscle contraction, mucus and blood vessel permeability changes, we use H1 receptor antagonists for the airway hyper-responsiveness and finally we can reduce exposure to triggers.

**Bronchodilators**

**B2 adrenoreceptor agonists.**

These act to cause bronchodilation. There is an increase in density of receptors as we move from the smooth muscle of the trachea to the small bronchioles. Other effects of these agonists include; the inhibition of the release of histamine and other inflammatory mediators. There is also a reduction in the vascular permeability and mucosal oedema.

**Adverse effects:** tachycardia (also effects the heart as it has some B2 receptors, but also acts on B1), palpitation and pulmonary vasodilation (B2 on blood vessels dilate).

The activation of the B2 receptor increases cAMP levels, which activates the K+ channel. This leads to the activation of the Na+/K+ ATPase, reducing the calcium dependent coupling of actin and myosin thus relaxing muscle. There is also inhibition of cholinergic neurotransmission.

We give these drugs by inhalation so as to avoid side effects. There are various types of drugs which all vary in specificity. The EC50 values range from $10^{-7}$ to $10^{-3}$.

### Short acting agents

- **Salbutamol**
- **Terbutaline**

- Maximum effect within 30 mins
- Duration action 3-5 hrs
- Used on a “as needed” basis

### Longer-acting agents

- **Salmeterol**
- **Formoterol**

- Duration action 8-12 hrs
- Given twice daily
- Adjunctive therapy in patients with chronic asthma where glucocorticoid therapy inadequate

### Non-selective β-adrenoceptor agonists

- **Isoprenaline**
- **Adrenaline**

Still used for severe asthma (STATUS ASTHMATICUS)

### Xanthine Drugs

**Theophylline**- given orally
Clinical use: Systemic glucocorticoids. Oral or intravenous indicated in several situations including acute asthma.

Oral: prednisolone vs prednisone
Prednisolone preferred as prednisone has to be converted in liver to active prednisolone except in pregnant patients where prednisone is not converted in foetal liver. Used if clinical situation deteriorates rapidly.

Intravenous: hydrocortisone. Used in acute / severe asthma. If lung function is less than 30% predicted following other treatments.

Cromoglicate and nedocromil

These are limited to use in asthma. They are weak anti-inflammatories due to short duration of action. If they are given prophylactically then they can reduce the intermediate / late phase asthmatic response and bronchial hyperactivity. The mechanism of action is unclear but they may reduce histamine release from mast cells.
need to flatten and become less cuboidal. In addition, the surrounding tissue needs to become highly vascularized and vessels need to closely associate with the epithelia. This is a slow process the 1st wave of maturation occurs at roughly 36 weeks and continues until about 8 years of life. This is the key factor in determining whether or not a premature baby will survive.

Surfactant is produced in the latter months of gestation. This acts to reduce surface tension and prevent alveolar collapse on expiration. Insufficient surfactant causes respiratory distress syndrome in premature infants. Surfactant is a collection of phospholipids and proteins. In the womb the foetus breathes in amniotic fluid so as to develop the respiratory muscles and stimulate lung development.

The lung is a mixture of endoderm and mesodermal tissues. The endoderm is the mucosal lining of the bronchi and epithelia of the alveoli whilst the splanchnic mesoderm forms the vasculature, muscle and supporting cartilage.

The diaphragm forms from the septum transversum. It rests between the yolk sac and cardiogenic area. There are small wholes in it to allow communication (these are the pericardioperinital canals). The cavity above the septum transversum will separate into 3 cavities; 2 pleural cavities and 1 cardiac cavity. This is achieved by pleural parietal folding; the cells grow into the body cavity and fold forming the 3 separate cavities.

The pleuroperitoneal folds invade and form the lateral wall. There is fusion with the oesophageal mesentery and septum transversum. The septum transversum forms the central tendon of the diaphragm. The lateral body wall forms the outer part of the diaphragm. The communicating wholes need to be sealed. If these don’t seal a congenital diaphragmatic hernia can form. Often these occur on the left side as this whole is bigger. The abdominal organs are pushed up into...
Cystic Fibrosis Symposium

Cystic Fibrosis (CF) is the UK's most common, life-threatening, inherited disease. CF affects over 10,000 people in the UK. The average life expectancy for someone with CF is ~40 years.

In the UK, 2.3 million people carry the faulty CF gene - 1 in 25 of the population. If both parents are carriers of the faulty gene, there is a 1 in 4 chance with every pregnancy that their child will have CF. CF affects vital organs in the body, especially the lungs and digestive system, clogging them with sticky mucus, which makes it difficult to breathe and digest food.

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Cystic fibrosis is a complex genetic disease affecting a number of organ systems including the lung and URT, the GI tract, pancreas, liver, sweat glands and genitourinary tracts. One needs to inherit two faulty alleles to have the disease since it is an autosomal recessive condition. It is the most common genetic disorder in Europe with an incidence of 1 in 2,500. This is due to mutation in the CFTR gene.

Life expectancy for those with CF has slowly risen and is now at about 40 years. The most common genotype in the UK (accounting for 90.7%) is the ΔF508 class 2 mutation. Class 2 mutations lead to defective processing of the CFTR protein.

66% of CF patients have a reduced FEV$_1$. These patients are highly susceptible to bacterial infections due to defects in the muco-ciliary escalator. Common pathogens include: *P. aeruginosa*, *S. aureus*, *H. influenzae* and *MRSA*. Chronic *P. aeruginosa* infections peak at ages 28-31 with roughly 65% of patients in the UK having this chronic infection.

All patients in the UK are registered so that their progress may be tracked.

Pathology

The main features are:

- Chronic lung disease
- Exocrine pancreatic failure
- Nutrition abnormalities [remember good nutrition of these patients is essential as it can help them fight infections]
- Intestinal obstruction
- Liver cirrhosis
- Male infertility
- Salty sweat [hence pilichloine sweat test – diagnose at over 60mmol$^1$]

Meconium Ileus

This is a failure for the new-born to pass meconium leading to plugging of the terminal ileum. This affects about 10-20% of patients. This can lead to distal intestinal obstructive syndrome, rectal prolapse and volvulus. There is little pathological change other than dilation and hyperplasia of sub mucosal glands.
drug has been approved for license.

**Presentation, Diagnosis and Course of Cystic Fibrosis**

CFTR is on chromosome 7 and there are more than 1800 mutation associated with the disease. The most common is ΔF508 with a 70% frequency in Caucasian populations. It is the most common life-threatening inherited disease. 80% of cases are diagnosed by 3. There are about 9,000 UK patients. The incidence in Caucasians is 1 in 2500 live births. It is a multisystem disorder.

CFTR controls chloride movement; the ΔF508 change occurs in the DNA sequence that codes for the first nucleotide binding domain (NBD1). The airway mucus become dehydrated as a result. Normally chloride is pumped out of the apical surface and sodium and water move from the mucus into the cell. Now chlorine isn’t pumped; but sodium and water still move into the cell. This makes dehydrated mucus.

About 15% of neonates will present with meconium ileus (acute intestinal obstruction, bilious vomiting and abdominal distension). This required medical and surgical assistance: an acetyl-cysteine enema is required along with laparotomy and resection.

In the infant feeding may be normal but baby may appear scrawny. There is failure to thrive. To investigate why: bloods, thyroid function, malabsorption screen [coeliac screen, sweat test and stool test for fat and faecal elastase]. The median age of diagnosis in 2003 was 7 months.

In the older child there may be increased suspicion that the child is underweight. The stools may be loose and smelly suggesting pancreatic insufficiency. Recurrent chest infections especially pneumonia are common. The chest may be deformed [Harrison’s scoli- shown on the right] and the digits clubbed. Clubbing is loss of the angle of the nail bed; increased nail curvature and sponginess of the nail bed.

In adults there may be classical symptom’s. There may be absence of the all classical features of pancreatic insufficiency and pulmonary disease. They could have pancreatitis with no other clear causes. Often there is recurrent sinusitis. It may come about in males due to infertility. In CF there is absence of the vas deferens leading to azoospermia. The atypical CF will not imply the same degree of morbidity and treatment expected in the classic disease.

There is now new born screening. This allows early detection; enable better treatment options and reduce anxiety by uncertainty caused by symptoms before a diagnosis is made. Screening is recommended but parents can refuse. Screening will miss some cases. Not all cases referred will have the disorder. Screening avoids long delays in diagnosis. Whilst early treatment may improve health but cannot prevent the progression of the condition. Treatment is with diet, medication and physiotherapy. Has been UK wide since 2007.
To confirm the diagnosis, do a sweat test (above 60mmol/l Cl, Na, or if there is more Cl than Na or if weight is above 100mg). Also do DNA testing. Also look for signs such as fat soluble vitamin deficiency (clotting problems, lack of vitamin E can cause anaemia, A and D lead to problems wit vision and bones).

In older patients to confirm maybe look at GI/liver problems, CF related diabetes, bone disease and allergic Broncho pulmonary aspergillosis.

When giving the diagnosis remember that most new-borns will be asymptomatic; so allow time for parents to come to turns with what is happening.

Patients need to visit the hospital every 6-8 weeks for nutrition and microbiological management. They need to be assessed for pancreatic sufficiency. Fat soluble vitamins (A, D, E and K) need to given. Twice daily physiotherapies needed. Prophylactic antibiotics [flucloxacillion and azithromycin] may have a role. Inhalers, nebulisers, mucolytic and steroids may all be useful.

Pulmonary lobectomy – used if there is established and severe localised bronchiectasis or persistent infection. 20% improvement in lung function within 6 months of surgery.

Survival rates are improving. This is due to many factors; use of multi-disciplinary teams, Dnase nebulisers to assist airway clearance, nebulised and IV antibiotics and avoiding BMI’s below 19.

Most UK children will now be diagnosed at birth from the screening procedures.

Nb Bronchioctasis is widening of the airway- this presents a risk of infection.