Cystic Fibrosis and Pseudomonas

Detailed History of Presenting Illness (HPI)

1st time:

diagnosed with cystic fibrosis (sweat chloride test) after presenting with

- **chronic cough**
- **abdominal pains**
- **salty sweat**

Subsequent Presentation: USUALLY RELATED TO INFECTION or COMPLICATION

- **difficulty maintaining body weight.**
- **Weight loss** despite use of enteral feeding at night.
- **frequent abdominal pain, cramps and bouts of diarrhoea.**
- **Recurrent chest infections** and hospitalisation
- **recurrent pneumothoraces**

Typically:

- **Cough**
- **Greenish Sputum**
- **Haemoptysis (!! Red Flag !!)**

List of Differential Diagnoses (DDx)

In a new CF case scenario: a positive sweat chloride test is unambiguous.

All newborns are now screened for CF.

In a known CF patient, the following pathogens must be considered:

in newly diagnosed CF patient

- *Staph. aureus*,
- *Strep Pyogens*
- *Haemophillus Influenzae*

in teenage CF patients

- *Pseudomonas aeruginosa*
- *Burkholderia cepacia*

List Pertinent Findings on History (Hx)

- **!! Get Vaccination Hx !!**
- **low grade fever,**
- **increasing cough** with sputum
- **worsening shortness of breath**
- **episodic haemoptysis**
- **sputum darkening and thickening** over recent days
  - Normally coughs up **1-2 cups of light green sputum daily**
  - **Sputum production is greatest in morning after Pt. has physiotherapy**
  - Occasional past episodes of **streaky blood in sputum**
  - Progressive exercise intolerance over several years worsening over recent months.
  - Exercise capacity reduced to walking around the house

List pertinent findings on Examination (Ex)

- Receiving oxygen through nasal prongs
- **Peripherally cyanosed** but not centrally
- **Gross clubbing** of digits
- **Use of accessory muscles** for breathing
- **Talking in short sentences only**
- HIGH RESPIRATORY RATE
- Probably mild thoracic kyphosis
- Chest size increased in the A-P diameter
- **Chest expansion markedly reduced bilaterally**
- Percussion note equal bilaterally

- Vocal fremitus and resonance equal bilaterally
- Breath sounds vesicular posteriorly,
  with **coarse crackles and high pitched inspiratory and expiratory wheezes** present throughout lung fields - not cleared with coughing

4

Cardiovascular Examination

- Expect a RAPID PULSE

Abdominal Examination:

- Expect splenomegaly and possible epigastric tenderness

Tests and Investigations

Investigating CF:

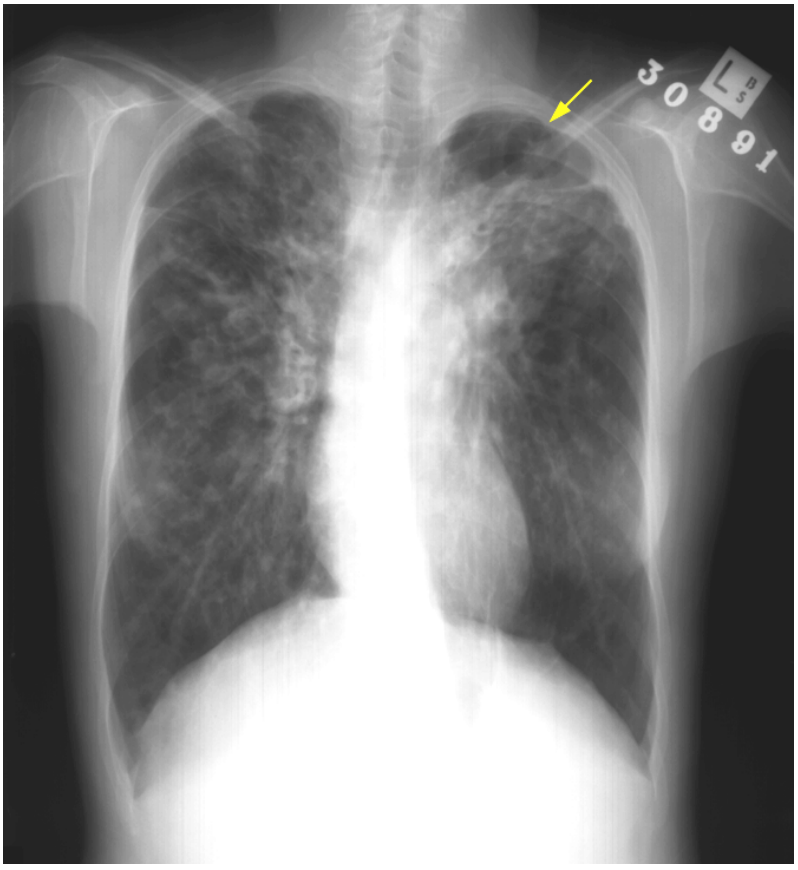
- At birth children appear normal.
  15% patients are diagnosed 24hours after birth from ***meconium ileus.***
  7% diagnosed > 18yrs
- **Suspect CF? → All newborns are now screened for CF.**
  = Immunoreactive trypsin / DNA analysis (10% misses.)
  Infants with **cystic fibrosis** 1 to 2 weeks of age show increased levels of **immunoreactive trypsin** in the plasma in the neonatal heal-prick test.
  - The test is positive if immunoreactive trypsin is greater than 80 mcg/litre.
  - It currently the best screening test for cystic fibrosis
  - It cannot be done after the first few weeks of life since it falls as pancreatic insufficiency develops.

OR = **Sweat test (>60mmol/L NaCl)**

Area of the skin (usually the forearm) is made to sweat by using a chemical called pilocarpine and applying a mild electric current
To collect the sweat, the area is covered with a gauze pad or filter paper and wrapped in plastic. After 30 to 40 minutes, the plastic is removed, and the sweat collected in the pad or paper is analyzed. Higher than normal amounts of sodium and chloride suggest that the person has cystic fibrosis

May not work well in newborns because they do not produce enough sweat.

Investigating the Cause of Haemoptysis:



STEP 1 IS CHEST X-RAY!!

← *The heart size is normal. There are marked changes of bronchiectasis present throughout both lungs. A large bullous air space is present at the left apex which remains unchanged from 2 months ago. No definite area of infective focus can be seen.*

GAS EXCHANGE: ABGs

Expecting:

- **LOW O_2**
- **LOW SATURATION (<90%)**
- **HIGH CO_2**
- **ACIDIC pH**
- **ELEVATED BICARBONATE**

ALL OF WHICH IS CONSISTENT WITH COMPENSATED RESPIRATORY ACIDOSIS

SERUM BIOCHEMISTRY: testing liver + kidney function

- In CF, expecting:
- **ELEVATED LIVER ENZYMES**
- **Will influence treatment if elevated beyond reasonable range**

ALSO: consider coagulation tests in hemoptysis

HEMATOLOGY: FULL BLOOD COUNT

- Expecting all normal except **ELEVATED ESR** due to continuous infective process

RESPIRATORY FUNCTION TEST: SPIROMETRY

- Expecting to see FEV1, FVC, and FEV1/FVC that **ARE DANGEROUSLY LOW**
- All findings well below the expected range

MICROBIOLOGY → SPUTUM CULTURE

Absolutely Necessary: need to know pathogen, sensitivities, resistances.
Nowhere as useful as in CF where pathogens are multi-resistant.
→ GRAM STAIN
→ SUSCEPTIBILITY CULTURES

Management

Goals:

1. **Delay/prevent disease progression (promote secretion clearance, control lung infection)**
2. **Attain optimal growth & nutrition (prevent intestinal obstruction, adequate nutrition)**
3. **Long term care: (not cure →there is no cure)**
4. **Psychosocial: Maintain Q of L child/ family, encourage independence, support**

1. Delay / prevent disease progression

A. **Promoting secretion clearance** (daily removal) → **Its ALL about the mucus**

- **Physiotherapy: encourage self-physio**
  - **Postural Drainage w/ percussion/ vibration:**
    - (position lobe/ aided by gravity/ percuss with cupped hand)
      - **Cannot do this to infants**
  - **Forced expiratory technique (FET):**
    - ½ huffs followed by breathing control,
    - **HOWEVER: FET alone will lead to desaturation**
  - **Active cycle of breathing technique:** Sequence of:
    - Breathing control
    - Thoracic expansion: 3/4, (w/ or w/o percussion/ vibration)
    - Breathing control
    - FET
  - **Positive exp. Pressure:**
    - Back pressure on expiration to
      - **increase collateral aeration of alveoli**
      - **reduce compression of airway**
  - **Flutter valve:**
    - Oscillatory ball inside device providing **back pressure and resonance to aid in shifting mucus**
  - **Exercise:**
    - improves general fitness, improved ventilation/ mucus clearance

- **Medications:**
  - **DNAse**:
    - large amounts of DNA in purulent secretions contribute to its viscosity
    - inhaled DNAse breaks down DNA in sputum; → improved clearance
  - **Hypertonic Saline**:
    - delivered intermittently during physio, **shown to THIN MUCUS**
    - hydration of airway→ improved clearance,
    - **HOWEVER:** trigger asthmatic response,
      - need to keep taking in order to improve.
  - **Acetylcysteine (Mucomyst):**
    - Breaks down DNA,
    - **HOWEVER: not shown to improve lung function**
    - Low compliance due to bad smell.
  - **Bronchodilators**:
    - Increase airway diameter; thus improve clearance
    - (B2 agonists, short/ long acting, alternative: Anticholinergic, short/long acting)
  - **Anti-Inflammatory drugs:**
    - **Corticosteroids**: Inhaled/ oral / I.V, contra's: doesn't improve irreversible component of lung function, risk of osteoporosis, bruising, cataracts, glaucoma
    - **NSAID's:** Ibuprofen high dose shown some benefits

B. Control lung infection (aggressive treatment):

- **Antibiotics:** chosen on sputum sensitivities
  - Oral, inhaled, I.V
  - I.V anti-Pseudomonas therapy ("tune-up's) as lung deteriorates and exacerbations accumulate

Respiratory Complications of Lung Infection

- **Haemoptysis:**
  - **Small volume:**
    - treat lung infection, assess coagulation and vit K status
  - **Massive volume**:
    - Bronchial artery embolisation (!! Drastic measure!!)
- **Respiratory Failure:**
  - **Med's:**
    - O2 supplementation: Nocturnal O2 therapy
    - nasal assisted ventilation,
    - Positive Airway Pressure
    - **HOWEVER all these measure show no affect on mortality**
  - **Surgery:** Lung transplant: the only treatment thus far,
    - 2-year survival >60%
    - transplanted lungs don't have CF
    - BUT: **!! graft rejection !!**
- **Pneumothorax:**
  - if < 10% of lung collapse: observe w/o intervention
- **Atelectasis**: reduction or absence of air in part or all of a lung,
  - → thus a reduction of lung volume
  - Chest physio, antibiotics

2. Attain optimal growth & nutrition (prevent intestinal obstruction, adequate nutrition)

- Gastroenterologist/ dietician:
- Nutritional assessment and advise
  - **Medications:**
    - **High calorie/ fat/ protein diet**
    - **Pancreatic enzyme** supplements before all meals
    - **Vit A, D, E, K.**
    - **PEG tubes** need to be considered if weight loss continues despite aggressive intervention.

3. Long term care: (not cure)

- **Regular check-up's:**
  - Symptoms/ signs
  - Growth
  - Lung function
  - Sputum
- Prompt recognition & treatment deterioration
- Med/ compliance review
- Reinforce multi-disciplinary team approach

4. Psychosocial:

Social worker/ Physician

- Maintain Q of L child/ family,
- **Education of child/ family**
  → encourage independence, thus:
  increased compliance,
  reduced deterioration

Support of child/ family: guilt, denial, stress associate

Lung Transplantation

- **Lung transplantation is the final therapeutic option** available for people with CF.
- **3 yr survival is about 60%.**
- Indications for transplantation are **patients under 60 years and a life expectancy of < 18mths.**
- No underlying cancer, systemic disease.
- **Mortality of CF lung transplant patients with Burkholderia cepacia infection is significantly higher** than lung transplant patients without Burkholderia cepacia infection.

Disease Definition

Cystic fibrosis (CF) is a monogenetic disorder that presents as a multisystem disease. The first signs and symptoms typically occur in childhood, but about 7% of patients in the United States are diagnosed as adults. This disease is characterized by chronic airways infection that ultimately leads to bronchiectasis and bronchiolectasis, exocrine pancreatic insufficiency and intestinal dysfunction, abnormal sweat gland function, and urogenital dysfunction. Patients usually die of respiratory failure.

Epidemiology

- **Incidence** :
  1 in 3000 Europeans,
- 1 in 17 000 Africans ,
- 1 in 90, 000 Asians
- Autosomal recessive disorder 1:22 people of European descent are carriers
  Age of onset: genetic disorder present from birth
  Sex prevalence: males same as females

Aetiology

Results from mutation of CFTR gene.
Resulting in 5 different classes of abnormalities in the CFTR protein(see cell biology for details.)
Mild mutant alleles are dominant over the severe mutant alleles and convey pancreatic sufficiency.

Prognosis

50 years ago, median survival <10years

Now,	@1993
Australia - **median survival 34 years**	North America – median survival 28.9 years
Females 27 years	Females 27.3 years
Males 41 years	Males 29.6 years

Over 95% CF die from respiratory failure

Predictors of mortality in CF patients

Poor prognosis	
Low FEV_1	Pneumothorax
Low $S_a O_2$ during 12min walk	Haemoptysis
High HR	Cor pulmonalae
Young age	Low blood Hb
Female	Airway hyperactivity
Low plasma albumin	Smoke exposure
Infections with P. areuginosa, Staph. aureus, Burkohlderia cepacia	

Pathophysiology

In lungs

- *Blocking of Cl^- ions moving out to lumen, raised Na^+ absorption from lumen and subsequent drawing in of Cl^- from lumen due to CFTR's inhibitory regulatory function of Na^+ channel activity.*
- Depletion of periciliary layer of water resulting in **thickening of mucus.**
- **Failure to clear** mucus.
- Site for **colonization by bacteria.**
- **Chronic infection**.

In sweat glands.

- Inability of sweat duct epithelia to reabsorb Na^+ and Cl^- ions from sweat secreted.
- **Therefore, sweat is highly salty.**

Pancreas

- Absence of CFTR in apical membrane of pancreatic ductal epithelium.
- Failure to secrete Na, HCO_3, and water.
- Retention of enzymes in pancreas,
- Destruction of pancreatic tissue.
- Beta cells usually spared but with age, type I diabetes may result.
- Malabsorption of proteins and lipids due to decrease digestion.
- Fatty stools.
- Fat soluble vit. E, K, A deficiencies.

GIT

- Lack of Cl^- and water secretions in intestinal epithelium.
- Failure to flush mucins in crypts.
- Excessive absorption of liquid in distal intestines.
- Leads to dessicated intraluminal contents and obstruction of small and large intestines.

- ***Meconium ileus-*** Obstructed bowel due to impacted, tenacious meconium, no air-fluid levels (probably due to adherent bowel contents). Occurs in newborns and there is an adult equivalent.

Genitourinary system

- Late onset of puberty for males and females.
- This is a secondary effect of chronic lung disease and inadeaquate nutrition.
- 20% of females are infertile and 95% of males are azoospermic.
- Congenital bilateral absence of vas deferens – 97% of CF males have this.
- Accounts of 1-2% of male infertility.

Basic Sciences and Comparitive Diseases

The CFTR protein is a single polypeptide chain containing 1480 amino acids that appears to function both as a **cyclic AMP-regulated Cl^- channel** and, as its name implies, a regulator of other ion channels.
The fully processed form of CFTR is found in the apical membrane in normal epithelia. Biochemical studies indicate that the ΔF_{508} mutation leads to improper processing and intracellular degradation of the CFTR protein. Thus, absence of CFTR at appropriate cellular sites is often part of the pathophysiology of CF.
However, **other mutations in the CF gene produce CFTR proteins that are fully processed but are nonfunctional or only partially functional** at the appropriate cellular sites.

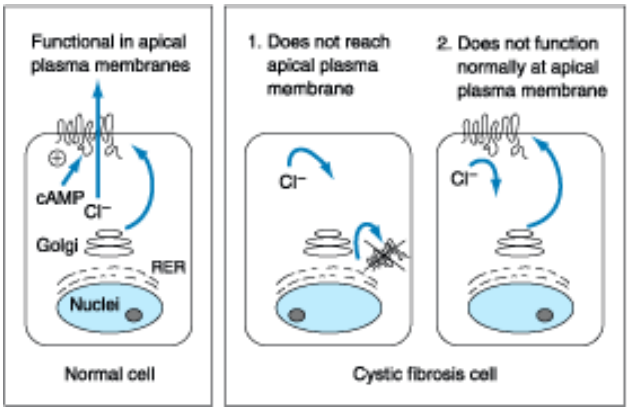


Figure 257-1: Cellular metabolism of the CFTR protein. **In a normal cell (*left*),** CFTR is synthesized in the rough endoplasmic reticulum (RER), is glycosylated in the Golgi apparatus, and functions as a Cl- channel and regulator of other ion channels when located in the plasma membrane. **Two possible outcomes of mutations in the CF gene are shown (*right*).** **(1)** If a mutation disturbs protein folding, e.g., the ΔF_{508} mutation, CFTR is degraded intracellularly so that no protein is transported to the plasma membrane. **(2)** With other mutations, the abnormal protein is processed and trafficks to the plasma membrane but functions abnormally at that site.

Biochemistry

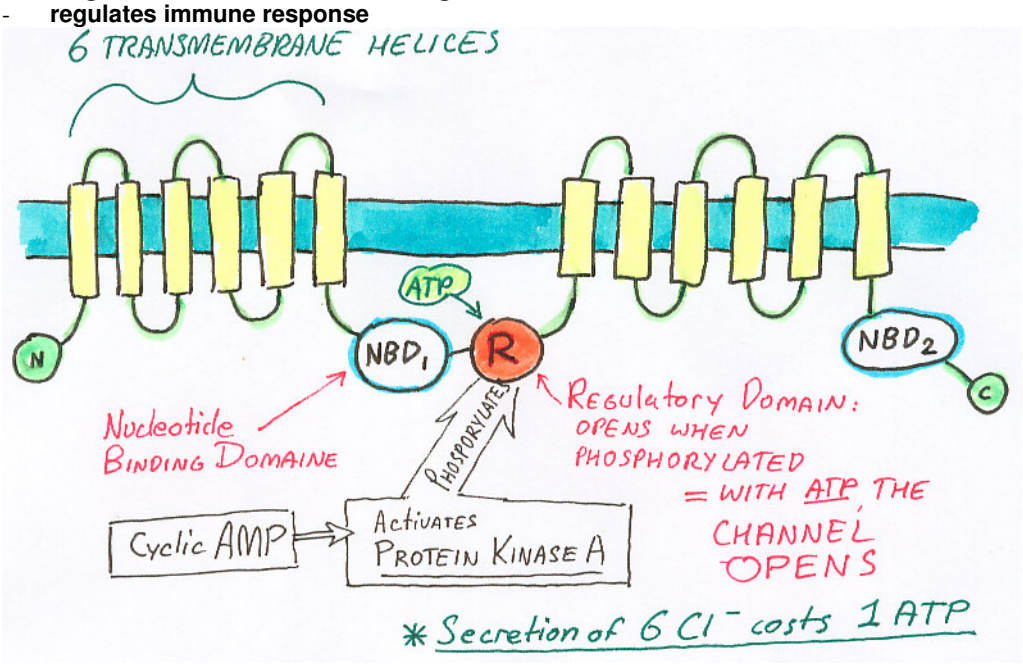
Classes of CFTR mutations.

Class I – defective protein; **no protein synthesis (! SEVERE !)**
Class II – defective protein processing; trafficking abnormalities
Class III – defective regulation of CFTR protein – 2nd messenger system or defect in binding/hydrolysis of ATP
Class IV – defective conduction through channel
Class V – reduced protein production by nucleus

CFTR protein is a cyclic AMP-activated Chloride Channel:

Also:

- Regulates the **CONSTRUCTION of the epididymis**
- **Begets Na^+ channels in the lung**
- **regulates immune response**



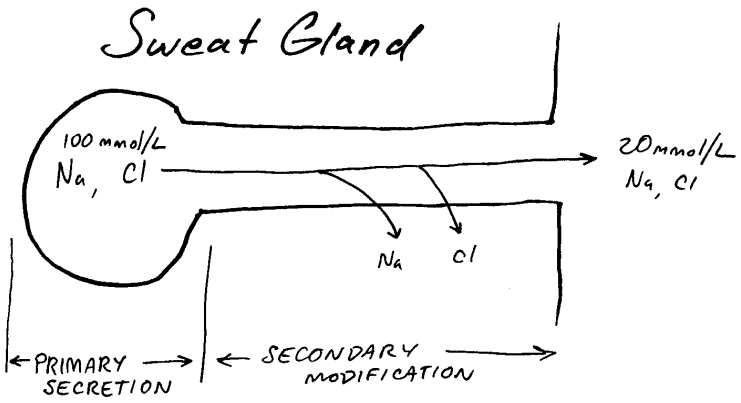
Cell biology

Sweat Gland

Normal biology.

Primary secretion:

by **sweat end piece cells (glands)**– secretion of Na^+ and Cl^- ions from secretory cells into sweat duct to be excreted.
Contains Ca^{2+} -activated Cl^- channel on apical membrane and $Na^+/2Cl^-/K$ co transporter and Na^+/K^+ ATPase pump on basolateral membrane of cell.
Transport of 3 Na^+ ions through the $Na^+/2Cl^-/K$ co transporter leads to the secretion of 6NaCl and hydrolysis of 1 ATP.
Activation of secretion is by acetylcholine which increases Ca^{2+} entry into cells and Cl^- channel opening.



Secondary Modification:

by **ductal epithelium**– Reabsorption of Na^+ and Cl^- ions from the ductal epithelium into cells

Cystic Fibrosis biology.

Primary secretory products normal

Secondary modification is impaired. CFTR channels on apical side of ductal epithelium not functioning properly. Resulting in high concentration of Na and Cl^- ions in ducts – high salt content of sweat.

Sweat end piece cells (glands) contain Cl^- channels which are Ca^{2+} -activated. Therefore no abnormality in primary secretion in CF.
Ductal epithelium contains CFTR channels. These are activated by protein kinase A and cAMP. Abnormality in secondary modification due to CRTR mutation in CF.

CFTR protein – two 6 transmembrane proteins linked together by R domain. R domain is phosphorylated by protein kinase A which is activated by camp. This Cl^- channel is thus activated by protein kinase A. Each trasmembrane protein is also bound to a **nucleotide binding domain (NBD)** which binds ATP. ATP binding regulates channel opening. When ATP in cells increase, channel opens. **Sweat secretion costs ATP**. For every 6 Cl^- ions, 1 ATP is used.

Frusemide – inhibits action of $Na^+/2Cl^-/K^+$ co-transporter. **Inhibiting secretion.**
Ouabain – blocks action of Na^+/K^+ ATPase pump. **Inhibiting secretion**
Amiloride- diuretic. Blocks Na^+ channel on lumen side of epithelial cell. Therefore no reabsorption of Na^+ occurs. Water remains in lumen of sweat duct.

Clinical features of CFTR mutation

Respiratory
Chronic obstructive lung disease, recurrent bronchitis, bronchiectasis, nasal polyps

Gastrointestinal
Pancreatic insufficiency, meconium ileus, diarrhoea, biliary cirrhosis.
Pancreatic sufficiency is preserved in 10-15% of CF patients

Reproductive
Male infertility due to CBAVD, subfertility in females
blocking of vas deferens, seminal vesicles and epidymuis result in obstructive aspermia

Signs and symptoms of inadeq ventilation- clubbing, cyanosis
Pancreas- inability of pancreas to secrete enzymes to breakdown fats which can result in diabetes and/or pancreatitits

GIT: probs due to inability to absorb nutrients, mucus plugging of intestines

Hepatosplenomegaly - from thick secretions blocking ducts and causing inflammation - to fibrosis

Osteoporosis- poor absorbtion of vit D and calcium

Arthropathy -- noted in lower limbs and fingers starting in adolescence, tends to be non- destructive, may be accompanied by fever and erythema nodosum

Genetics

The CFTR (cystic fibrosis transmembrane conductance regulator)gene is found on chromosome 7q13 consisting of 27 exons over 250kb of DNA.

Most common mutation (>75%) is delta F508 in Northern Europeans:

- resulting in ineffective synthesis of protein.
- >800 other less common mutations (2%)

Variation in the mutations make DNA dianosis and screening for CF very difficult.

Phenotypic variants

Genetic heterogeneity results in clinical heterogeneity in which multiple CF related phenotypes can be explained by different types of mutations which are present. Eg. Congenital bilateral **absence of vas deferens**, **bronchiectasis** or **pancreatitis**.

Genotype: Phenotype variations

Severe mutations correlate with pancreatic insufficiency but do not correlate well with pulmonary disease/ Mild mutations confer pancreatic sufficiency

Intrafamilial variations exist even with same genotype

Splicing variants have variable effect.

CFTR splicing variants

Intron 8 5T sequence causes removal of exon 9 which decreases amount of normal CFTR produced. If >25% of CFTR is normal, lung function will be normal.

Mutational analysis –

by positional cloning(isolating the gene before discovering function of it's protein by linkage analysis).

- **80% detection rate of CF.**
- Mutation type is dependent on ethnicity.
- Only test for carrier status if indication exists.

Mutational scanning – to find mutations in CFTR gene. Time consuming and costly.

Importance of taking thorough family history.

Hardy Wienberg Equation

$$p^2 + 2pq + q^2 = 1$$

p^2=incidence in population

p= frequency of mutant allele

q= frequency of normal allele

2pq= carrier frequency

In Northern European population, incidence=1/2500= p^2

p = 1/50

q = 49/50

Carrier freq, 2pq = 1/25

Behavioural Sciences:

Uncertainty in illness

Patient features associated with uncertainty

- Lack of adequate information
- Information overload
- Individual response to stress

Stress Schema

1. Stressor exposure
2. Appraisal
3. Stress response

Search of Homeostasis

1. Adaptive/Maladaptive Coping
2. Problem focused coping
3. Emotion focused coping
4. Coping styles

Defense coping styles

1. Adaptive eg. Humour
2. Rationalization eg. Withdrawal
3. Maladaptive eg. Projective identification
4. Pathological eg. Delusional beliefs

Cystic Fibrosis NSW

Support services for patients and families of CF

Counselling support for families and patients

Financial assistance

Youth programs – however, outings have been limited due to need to limit spread of infection from patient to patient

Fertility clinics for men and women – IVF centres

Transplantations

Terminal stage support

INITIAL MUTATION OF CHLORINE CHANNEL (affects Type II alveolar cell)
Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene - locus at chromosome 7q13
MOST COMMONLY: deletion of **Phe @ nucleotide binding site**
(resulting in CFTR never making it to the membrane)

Secondary modification of sweat is impaired; thus **MORE SALT IN SWEAT**

Increased water absorption causes pancreatic ducts to become clogged with mucus =hence, **PANCREATIC INSUFFICIENCY**

Defective CFTR fails to regulate the development of a Vas Deferens; **THUS: STERILITY + ASPERMIA**

Decreased absorption of Cl, thus **Increased absorption of Sodium** Thus **INCREASED ABSORPTION OF WATER FROM ALVEOLAR LUMEN**

Increased MUCUS VISCOSITY

Decreased MUCUS CLEARANCE

Pseudomonas Aeruginosa
Colonises the poor wretch's lungs taking advantage of impaired clearance

CIRRHOSIS of the LIVER
Results from hepatobiliary canaliculi becoming blocked with thick mucus
+ PORTAL HYPERTENSION
due to liver disease
-results in **SPLENOMEGALY** as spleen is inflated by increased blood pressure

Lipopolysaccharide is detected by TOLL-LIKE RECEPTORS on epithelial cells, plus MACROPHAGES and NEUTROPHILS

Immune Response ensues
Neutros and Macros arrive into the alveolar lumen
-destroying the basal lamina in the process
Thus weakening the bronchus

continuous coughing and recurrent infections cause the weakened damaged bronchus to balloon out, forming saccular air spaces
=BRONCHIECTASIS,
=very specific finding for CF
a perfect situation for bacterial colonies to prosper

REACTIVE OXYGEN SPECIES
- Effect a phenotype switch, causing the pseudomonas to produce copious amounts of alginate slime

In the thickened mucus and alginate slime, A MICROBIAL BIOFILM IS FORMED
- is thick slime, made up of
- **10% to 20% bacteria**
- **80-90% mucoid alginate**

ALGINATE: an unbranched linear polysaccharide
Penetrated by minute anastomosing water channels, a primitive circulation
= **has been a bacterial defence mechanism since the Pre-Cambrian**

Acquisition of ANTIBIOTIC RESISTANCE
CF patients continuously exposed to multiple combinations of antibiotics

Advantages of Biofilm:
- **Conveys protection** from **cough clearance**
- **Protects from antibodies, antibiotics, and phagocytes**

Pharmacology

CF sufferers are among the MOST MEDICATED PATIENTS, with up to fifty pills per day

To relieve Bronchoconstriction:

- Bronchodilators– **beta agonists, anticholinergics.**
- Both can be used together to get additive effect.
- **Eg. Salbutamol**

Inflammatory stage of illness:

- Anti inflammatory drugs may be of some use
- Eg. Aspirin, selective COX2 inhibitors

Frusemide – inhibits action of $Na^+/2Cl^-/K^+$ co-transporter. **Inhibiting secretion.**
Ouabain – blocks action of Na^+/K^+ ATPase pump. **Inhibiting secretion**
Amiloride- diuretic. Blocks Na^+ channel on lumen side of epithelial cell. Therefore no reabsorption of Na^+ occurs. water remains in lumen of sweat duct.

Antibiotics

– **empirical**(treat without susceptibility testing) therapy usually employed first.

- **combination antibiotic therapy is usually employed**. The combination of antibiotics used depends on the doctor's experience, hospital guidelines and microbiology lab. testing.
- **Antibiotics usually given for longer than normal**
- **and in higher does than other respiratory diseases.**
- **IV and inhalation routes used.**
- Cephalosporins, quinolones, aminoglycosides used.

Oxygen therapy given to manage respiratory failure.

- Nocturnal oxygen therapy usually with BPAP.

Dnase

- to breakdown DNA in mucus filled lung airways to thin the mucus.
- Enable ciliary action of airway epithelium to remove mucus.

Hypertonic saline

- is also used to thin the mucus by osmosis of water out from epithelial cells into lung airway lumen.

Oral pancreatic enzymes

- Pancreatic insufficiency treated by taking **oral pancreatic enzymes** before all meals.
- Pancreatic Enzymes – pancreatase.

Physiology

Info re. Stretch, pain, touch is transmitted from the lower respiratory tract by the afferent fibres in the autonomic nervous system

Innervation of pleura::

- **Parietal pleura:**
- Costal pleura: intercostal nerves
- Diaphragmatic pleura: phrenic nerves, lower intercostal nerves
- Mediastinal pleura: phrenic nerve
- **Visceral pleura:** vagus nerves and sympathetic trunks form the pulmonary plexuses

Innervation of LUNGS: vagus nerves and sympathetic trunks
THUS, VISCERAL PLEURA SHARES THE INNERVATION OF THE LUNGS.

Chronic cough (>3 wks)– due to chronic bronchitis, asthma, post-nasal drip, gastro-oesophageal reflux or bronchiectasis.

Acute cough = (< 3wks)

What is the cough reflex?
Cough is an important normal protective reflex activity

Cough receptors most numerous at the carina and points of bifurcation of bronchial tree.

- **Rapidly adapting receptors**, RAR (irritant receptors), main mediators of cough.
- Stimulated by mechanical, chemical and inflammatory stimuli.
- Sensitivity to these stimuli vary according to site of stimulation.

afferent nerves, (trigeminal, glossopharyngeal, superior laryngeal, vagus)

- **Unmyelinated C fibres** cause direct inhibition of cough through gating mechanism.
- **Bronchial C fibres** indirectly induce cough by **neurogenic inflammation** through release of inflammatory mediators including bradykinin and tachykinins which stimulate RARs.
- **Pulmonary C fibres** and **slowly adapting receptors** regulate cough.

a poorly defined cough center, @ medulla oblongata

- **Stimulation is via myelinated fibres to cough centre in medulla oblongata**.

efferent nerves: (recurrent laryngeal nerves, vagus, corticospinal tract + peripheral nerves)
effector muscles.

Reflex begins with **deep inspiration**, followed by **glottic closure**, **diaphragmatic relaxation**, and **thoracic and abdominal expiratory muscle contraction**. About 0.2 seconds after glottis closure, it reflexively opens with resulting turbulent expiratory flow.

Posterior wall of airway invaginates and causes shearing of mucus. Positive pleural pressure generated up to 100-300 mm Hg; peak flows of 12 L/sec

Microbiology

COMMUNITY ACQUIRED PNEUMONIA

TYPICAL		
MICROORGANISM	CLINICAL & RADIOLOGICAL	MICROBIOLOGICAL DIAGNOSIS
Streptococcus pneumoniae	Lobar pneumonia	Gram stain sputum; culture sputum and blood
Haemophilus influenzae		Ditto
Staphylococcus aureus	Post-flu, IV drug use	Ditto X-ray shows abscesses

ATYPICAL		
MICROORGANISM	CLINICAL & RADIOLOGICAL	MICROBIOLOGICAL DIAGNOSIS
Legionella pneumophila **(and other species)**	"Damaged" lung (e.g. smokers)	Immunofluorescence of sputum for Legionella antigen; culture of sputum on BCYE media; serology (by immunofluorescence)
Mycoplasma pneumoniae	Adolescence	Serological: 1. cold agglutinins (not specific) and 2. complement fixation
Chlamydia psittaci ***Chlamydia pneumoniae*** **(TWAR agent)** ***Chlamydia trachomatis***	Contact with birds Neonates only	ALL SEROLOGICAL (by complement fixation)
Mycobacteria	M.t.b: cavitatory disease etc.	Acid Fast Bacilli Culture on L-J media
VIRAL **Adenovirus** **Influenza A** **Herpes varicella/zoster** **Respiratory Syncitial Virus**		ALL SEROLOGICAL (by complement fixation) Immunofluorescence for antigen in nasopharyngeal swab

Bacterial causes of lower respiratory tract infections in CF patients

Staph. aureus*, *Haemophillus Influenzae in newly diagnosed CF patient
Pseudomonas aeruginosa **and** ***Burkholderia cepacia*** in teenage CF patients
50% CF patients with Aspergillus fumigatus (fungi)

Many of the bacteria are resistant to multiple antibiotics. Therefore use of MCBT (multiple combination bacterial testing) is done in severe cases of respiratory failure to treat infection.