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REVIEW OF CYSTIC FIBROSIS

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***Abstract*--CF is a lifelong genetic disease that result in formation of thick, sticky mucous in lung, pancreas and other organs. In lung, the airway is blocked by mucous causing lung damage. CF is as a result in mutation in cystic fibrosis transmemebrane conductance regulator (CFTR). The most common mutation in CF gene is (ΔF508). In ΔF508 mutation the Δ is deleted from three nucleotides result in loose of phenyl alanine amino acid at 508th location on protein. CF caused by mutation of (ΔF508) account two third of cases worldwide and difficulty in breathing and eventually severe lung infection.**

The most common signs is salty skin, growth rate retardation and loss of weight, however the food intake is normal, accumulation of thick sticky mucous in chest region which is difficult to control because of it's sticky in nature. Different diagnosis categories are used in screening of CF, such as sweat test or genetic testing and new born screening. In new borns, measuring the level of immunoreactive trypsinogen is valuable in detecting CF.

Although there is no healing in CF patients, many ways are available for treatment. The key role in management of CF is treating of airway infection and encourages the patient to an active life style and using high energy content food. Management of CF continue throughout patient's life and it is important in maintaining of organ functioning and delay organ dysfunctions

Index Terms **Cystic fibrosis (CF), cystic fibrosis transmemebrane conductance regulator (CFTR), ΔF508 mutation**

I. INTRODUCTION

CF is a lifelong genetic disease that result in formation of thick, sticky mucous in lung, pancreas and other organs. In lung, the airway is blocked by mucous causing lung damage and difficulty in breathing and eventually severe lung infection. In pancreas the most common feature is obstruction of pancreatic duct, which is lead to limitation in passage of pancreatic enzyme resulting in digestive problems (*cystic fibrosis foundation 2007*).According to many surveys which have been done by health organizations, survival age from CF has improved significantly over past 50 years, with increasing of median age of death by CF (*Elborm, 2000 and Dodge, 2007*). This improvement has been attributed by several factors including nutritional improvement, early monitoring of the individuals with early symptoms of CF and using drug of choice for treatment (*Farrel, 2005 and Merel, 2001*). In addition, socioeconomics play an important role in survival improvement with CF over 20 years ago. Children in England and Wales were found from manual socioeconomic groups have rate of death by CF three times more than those from non-manual socioeconomic groups (*Britton, 1989*). CF is caused by mutation in genes that encode cystic fibrosis transmembrane conductance regulator protein, which is expressed in many epithelial cells and blood cells (*Reisin,1994 and Mehta, 2005*).CF is vary between patients and even children of same CFTR

genotype and polymorphism. Severe pulmonary disorder with evidence of gene to gene interaction has been shown that result from polymorphism in transforming mannose binding lectin 2 gene and growth factor B1(*Drumm, 2005 and Collaco, 2008*). Epidemiologically, Northern European decent is more commonly affected with CF, in which approximately 1 in 3000 birth (*Walters, 2007*). In addition the prevalence of CF is vary from country to country and depends on ethical background, for example the incidence of CF in white American is higher than Latin American and the incidence of CF in African American is very low comparing to other ethical backgrounds (*Drumm, 2005*). Microbiologically, *Haemophilus influenza*, Staphylococcus *aureus* and *Pseudomonas aeroginosa* are the most frequently founded bacteria in airway of patient with CF (Govan, *1990* and *Van Schilfgaarde 1999*). Among those infectious agents, *Pseudomonas aeroginosa* regarded as a common and highly causative agent of CF by its appearance in 27% patients with CF aged 2-5 years and 80% in those of 25-34 years (*Cystic fibrosis foundation 2005*)

A. Causes;

CF is result in mutation in cystic fibrosis transmemebrane conductance regulator (CFTR). The most common mutation in CF gene is (ΔF508). In ΔF508 mutation the Δ is deleted from three nucleotides result in loose of phenyl alanine amino acid at 508th location on protein. CF caused by mutation of (ΔF508) account two third of cases worldwide (*Mitchell, 2007*). CF can be prevented in those who have only one copy (alleles) of CFTR gene. Although most of the people have two copies but when none of the copies produce functional CFTR, CF develops thus it is regarded as an autosomal recessive disease. CFTR is located in 931.2 locus chromosome, and it is 230,000 base pairs in length which produce a protein with 1,480 amino acid length. CFTR genes produce a halide anion channel which is important in sweat, digestive juice and mucous secretion and by having ATP-hydrolyzing domain CFTR allow protein to use energy in form of ATP and it possess tow domain which is used by protein to across the cell membrane. In addition, there is increasing evidence that genetic modifiers besides CFTR modulate the severity and frequency of the disease such as mannan-binding lectin, which is involved in innate immunity by accelerating phagocytosis of microorganisms. Polymorphisms in one or both mannan-binding lectin alleles that result in lower circulating levels of the protein are associated with a threefold higher risk of end-stage lung disease and increased burden of chronic bacterial infections (*Mitchell, 2007*).

B. CFTR function;

CFTR is regarded as a member of family of transmembrane protein known as (ATP) binding cassette transporter and in apical membrane its function to transport chloride (*Schwiebert, 1998*). Chloride secretion becomes abnormal when CFTR affect on chloride channel in CF individuals (*Quinton, 1983*). In addition CFTR has other function like regulating other membrane channel such as epithelial sodium channel (*Reddy, 1999*), regulate $HCO3^-$ transporting through epithelial channel and CFTR considered as a channel for glutathione protein (*Quinton, 2001and Riordan, 2008*). CFTR has interaction with many intracellular protein but the relevance of this interaction not fully understand (*Wang, 2006*), but this interaction has its importance in therapeutic enhance to chloride secretion.

C. Signs and symptoms of CF;

CF is holistic diseases, i.e. result in several organ impairment in the body with differences in severity and out coming of the condition. The most common signs is salty skin (*Quinton, 2006*), growth rate retardation and loss of weight, however the food intake is normal (*Hardin, 2004*), accumulation of thick sticky mucous in chest region which is difficult to control because of it's sticky in nature (*De Lisle, 2009*), coughing is frequent with incidence of chest infection and shortness of breath (*O'Malley, 2009*). In male symptoms include infertility which is account in 97% of men with CF are infertile, in those men sperm production is normal but missing vas deference make them infertile but recently study showed that they could have baby with assistance of reproductive techniques (*McCallum, 2000*). In women, thickening of cervical mucosa and malnutrition cause difficulty infertility and in severe case malnutrition may cause disrupt of ovulation (*Gilliam, 2000*). In children the most common symptom is meconium ileus and when they grow the need more exercise to eliminate sticky mucous in alveoli (*blackman, 2006* and *Ratjen, 2009*). Mutation of protein in some patient leads to change in mutated epithelial cells and abnormality in mucous viscous production (*De, 2009*). In CF growth failure is related to multi factor including; abnormality in food absorption in GIT and chronic lung infection due to accumulation of mucous substance (*Hardin, 2004*). Coagulation disorder particularly during foetal life is another symptom of CF. In young children vitamin K absorption is impaired due to sensitivity of young children to vitamin K absorption and very small amount of vitamin K across placenta result in low reserve of vitamin K. As a result of Clotting factors (II, VII, IX, and X) highly vitamin K dependent, coagulation problem is happen due to low level of vitamin K (*Reaves,*

2010). In pancreatic disorder by CF, both type of diabetes could be seen due to damage of Langerhans cells that responsible for insulin production and blood sugar regulation (*Alves, 2007 and Haworth, 1999*). In addition poor vitamin intake because of malabsorptoin which is require for calcium and phosphorous regulation cause bone weakness and osteoporosis which is highly susceptible to fracture (*Haworth, 1999*).

D. Pathophysiology;

Pathological changes by CF depend on onset and complication of CF and degree of mutation of CFTR.

1) . Respiratory system:

In individuals with CF, the most common pathological change in respiratory system is pneumonia or haemoptysis due to acute respiratory failure. *Pseudomonas areoginosa*, *Haemophilus influenza and Staphylococcus aureus* are the most common cause of pneumonia in patient with CF. It has shown that PH level of the cells in patient with CF is different from those without CF and this difference increase Asailo Gam 1 molecule which is a receptor for bacteria in respiratory system and resulting in colonized airway with *Pseudomonas aerginosa* as CFTR binding decrease (*Schweibert, 1998*). In some patients with CF, pneumonia results in infection by *Pseudomonas cepacia*, which quite difficult to manage because it's highly resistance against most antibiotics. In individuals with CF, when pneumonia progress, inspiration and expiration of air become difficult, leading to obstruction of airway and alveolar expansion due to accumulation of air and pulmonary parenchymal destruction which result in increase pulmonary arterial pressure and eventually right side heart failure, which In this case pulmonary functioning test is necessary to detect the amount of destruction by CF. One of the parameters is forced expiratory volume (FEV) in one second for measuring the onset of the destruction by CF. If (FEV) is low in individuals with CF, it means further complication of the destruction by CF (*Hart, 2002*). Moreover, interleukin-10, which has anti-inflammatory property, is decrease and severe inflammation after infection is obvious especially in lungs (*Saddane, 2005*). In some cases, persistence of lung inflammation changes from acute to chronic and causing hypertrophy of bronchial artery and eventually haemoptysis. Study showed that, haemoptysis in CF caused by malabsorption of vitamin K because of frequent using of antibiotics (*Antonelli, 2002*). In approximately 10% of individuals with CF may have infection with fungi *Aspergillus fumegutus?* This infection cause pulmonary aspergillosis and massive increase in secretion which is very thick in nature and not affected by antibiotics (*marchand, 2001 and Elphick, 2000*). Pulmonary aspergillosis remains Asymptomatic until

bronchopulmonary mycosis developed, but on screening mutation of CFTR are found.

2) . Haematopoietic system:

Generally, in patient with CF anaemia develop as a consequence of colonization of *Pseudomonas aeroginosa* and haemoptysis (*Stites, 1999*). The patient lost blood through bleeding result from hypertrophy and tortuous of bronchial artery due to chronic inflammation. Iron absorbed by inflammatory infectious agent (*Pseudomonas aeroginosa*) for their growth and development, in addition, P aeroginosa result in further iron lost through sputum and bronchial airway fluid lavage which they are highly iron containing (*Taussig LM 1999).*

3) GIT system;

GIT problem in patient with CF, result in abnormality in pancreatic enzyme secretion to digest the food. Impairment of pancreas leads to secrete abnormal nature of secretion which is thick mucus in nature and obstruction of pancreatic duct, thus the amount of enzyme that can be secreted is not sufficient to digest food which is taken by patients. Malabsorption and inadequate absorption of fat soluble vitamins A, D, E, K is a consequence of less amount of pancreatic enzyme inter into intestine. Study shown that in CF, supplement and vitamins should take separately, because supplement taking in many patients with CF may result in impairment of iron absorption (*Stites, 1999*). Loss of appetite, abdominal pain, vomiting and decrease in peristaltic movement are the common manifestation of individuals with CF, because of dilatation of intestine and filling with faecal content (Taussig, *1999*). Faulty secretion of salt and water in distal part of intestine cause distal intestinal obstruction syndrome which is make intestinal material dehydrated and in some patients gastroesophageal reflux might see due to low bicarbonate secretion and hyper secretion of gastric juice.

4) Endocrine system:

The primary complication in CF diabetic related is deficiency of insulin because of pancreatic duct obstruction which is account approximately one in 10 of individuals with CF. HBAc1 test which is used to monitoring of glucose amount in diabetic patient is not accurate in patient with CF, because of rapidly in turnover of RBC in patient with CF. The problem is patient with CF related diabetes still need high energy diet which is opposite to the quality of diet used by diabetic individuals. In CF related diabetes, glucose metabolism accelerated by many factors including (liver dysfunction, dehydration, malabsorption and frequent infection (*Moran, 1999*).

5) Sweat glands:

CF patients lost excessive salt after exercise or heat due to low level of CFTR in body which is

responsible for regulation of salt in sweat and this result in weakness, lethargy and loss of appetite.

6) Reproductive system:

In most of men due to absence of vas deference or malformed, reproductive capacity impaired and they become sterile. While in women, they could become pregnant but the gestation period is longer than its in normal women because of reduce in sperm movement in cervix and oviduct due to presence of thick mucus substance (*Taussig, 1999*).

E. Genetics:

In past few years after CFTR gene defect detected, it was believed that CF cause limited number of diseases causing mutation. By the time approximately 1500 different mutation has been detected, but the majority of those genes are rare and functional consequence of many of them is poorly understood (*Riordan, 1989 and Rommens, 1989*). Indeed less than 10 mutations occur with a frequency of more than 1%, while in patient with CF approximately 66% cases result in deletion of phenyl alanine in $\Delta 508^{th}$ location. Depending on functional consequence of CFTR with in cells, CFTR mutation can be grouped into different classes; CFTR either not produced (1), insufficiently produced (2), randomly arranged (3), showed abnormal conductance (4), its production partially defective (5) or has enhanced degradation (6) (*The cystic fibrosis mutation database 2009*). In pancreatic insufficiency class (1, 2) and 3 mutations are more common, while in class (4, 5, and 6) mutation pancreatic function is normal (*Collins, 1992 and Rowe, 2005*). Knowledge about genetic abnormalities in detail essential to find a target for therapy for example ΔF508. CFTR is abnormally folded and identified as abnormal protein in endoplasmic reticulum and it is degraded in proteasome protolytically (*Ratjen, 2007*). The amount of ΔF508 CFTR which is reach to epithelial cells is small, however its functionally active but their half life in plasma membrane is generally reduced (*Cheng, 1990 and Bear, 1992*), which believe that rescue of ΔF508 CFTR interference with pathways that recycle CFTR in plasma membrane or rescue form endoplasmic reticulum may be the strategy of treatment (Okiyoneda, *2007).*

F. Diagnosis and monitoring;

Different diagnosis categories are used in screening of CF, such as sweat test or genetic testing and new born screening. In new born, measuring the level of immunoreactive trypsinogen is valuable in detecting CF (*Daves, 2007*). Trypsinogen level elevated in individuals who have one copy of mutation in CFTR gene or some time trypsenogin level elevated in individuals even with two normal copies of CFTR gene, for this result new born screening causing disagreement (*Ross, 2008, Assael, 2002*). In most states or countries they do not perform screening for CF and the individuals diagnosed after

symptom appearance (*Michell, 2007*). In general, sweat test is a common test in screening of CF; it's done by applying medicine that enhances sweating (Pilocaroine). Iontophorosis is used to deliver the medication through the skin in which one electrode placed on skin and electrical current passed through it and another electrode placed on to applied medication. After that delivered sweat collected in a capillary tube or on filter paper to detect the amount of sodium and chloride. In CF case, the amount of sodium and chloride increased while the amount of thiocyanate decreased in their saliva (*Minaroski, 2008*). In individuals with pulmonary symptom related to CF, X-ray and CAT scan are used to detect the size of infection and damage of lung. Bacterial examination of sputum is required for detecting the organism which causes infection of lower respiratory tract. Blood test is also used in diagnosis of CF by detecting vitamin deficiency and liver function. Insufficient digestive enzyme due to pancreatic damage could be detected by using DXA scan for testing faecal elastase. In mild form mutation of CFTR gene, sweat test is insufficient in diagnosis of CF because the change of chloride concentration is less than (60 mM/L), in this case nasaltransepithelial potential differences (TEPD) are commonly used. Abnormalities in exocrine glands related to CF, cause increasing in water and sodium reabsorption and reduction in chloride secretion, these change result in higher TEPD than normal which is used as a useful form of diagnosis in people with mild form of CF (*Freudenheim, 2009*).

G. Prenatal:

CFTR genes mutation in couples who are pregnant or planning to pregnancy is important to detect the degree of risk on baby after birth. Screening of foetus not performed unless parents were tested and the risk of CF was found high (*American college of obstetricians and Gynocologists and American college of genetics 2001*). CFTR gene mutation screening initially performed to one of parent and if the test result show carrier of CFTR gene mutation the other parent tested to calculate the degree of risk of baby with CF after birth because CFTR test is expensive and CF progression in foetus needs to pass a mutated copy of CFTR genes. More than thousand different mutation cause CF and testing for each of them is impossible due to its time and cost effectiveness but for those with ΔF508 mutation it must be performed because this type of mutation is regarded as a common cause of CF. specific screening performed for individuals with known uncommon form of mutations because not every negative results means the child is free form CF (*Elias, 1991*). In addition screening commonly performed with higher risk of mutation but for those of low risk ethnicities is less common because in general population the mutation in low

risk ethnicity is less common. In embryonic transplantation further tests performed for couples with higher risk of CF by invitro fertilization and screening the fertilized embryo after 3 days for detecting abnormal CF genes. If only one of the mutated CFTR genes are recognized the embryo implanted but if two mutated genes recognized the embryo is not transformed. Although tests performed on placenta (chorionic villus sampling) result in death in 1% of amniocentesis and 1 in 200 at gestation period, placental and fluid around foetus screening are performed (*Tabor, 1986*). Economically preimplanted genetic diagnosis (PGD) in carrier couple of CF is limited by age and it is valuable until maternal age of 40, after that period, abortion and natural conception has higher economic benefits (*Daves, 2010*).

H. Management;

Although there is no healing in CF patients, many ways are available for treatment. The key role in management of CF is treating of airway infection and encourages the patient to an active life style and using high energy content food. Management of CF continue throughout patient's life and it is important in maintaining of organ functioning and delay organ dysfunctions. Treatment of CF occurs at specialist multidisciplinary centres because of wide variation in disease symptom and the target organ for therapy are GIT including (pancreatic enzyme supplements), reproductive organs and lungs (*Daves JC 2007*). In CF, the most important aspect of management is early treating of lung damage caused by thick sticky mucous which is limit lung function and movements. Oral antibiotic administration or inhaled antibiotics used to treat infection and thick mucus substance in respiratory airway could be removed by using mechanical devices or inhaled medication. In general early diagnosis of individuals and using a drug of choice are the best way in management of CF.

1) Antibiotics:

In many patients using one or more antibiotics is normal even if they are considered healthy in order to protect them and suppress the infection. Antibiotic using in those with pneumonia caused by CF is very important especially in those with in adequate lung function and the antibiotics have been chosen based on analysis of sputum and history of response. Occasionally some strains of bacteria that cause CF, are not easily treated with only orally administration route, long term intravenous of antibiotic administration is require such as (Ciprofloxacin, meropenem, tobramycin, vancomycin and piperacillin). This long term of treatment some time require permanent IV insertion in hospital such as peripherally inserted central catheter (PICC line). Lung function might be improved by using long term of inhaled therapy with antibiotics such as (cayston, colistin

and tobramycin) by imbedding of colonized bacteria (*Pai, 2001, Westerman, 2004 and McCoy, 2008*). Additionally, ciprofloxacin or azithromycin are orally administrated for prophylactic strategy or for control of infection *(Hansen, 2005*). Long term using of Aminoglycosides (tobramycin) can result in several dangerous side effects like imbalance in inner ear, hearing loss and kidney problem, in this case to minimize the side effects amount of antibiotics in blood should be measured regularly (*Tan, 2003*).

2) . Other treatment for lung abnormalities:

Generally in pulmonary form of CF, removing of sputum and encourage of its expectoration is very important. Chest physiotherapy is used for those in hospital setting and the secretion is loosen up by the percusses of the patient's chest with their hand several times daily. Intrapulmonary percussive ventilator and THAIRapy vest are used for recreating percussive therapy. Recent methods such as; associated clearance mode and Biphasic cuirass ventilation integrate in cough assistance phase and vibration phase for removing of secretion (*Van der, 2000*). Dornase Alfa and hypertonic saline (areolised medication) are used in loosen of secretion (*Kuver, 2006*). Dornase has effect on sputum by breaking down of DNA in sputum and decreasing its viscosity (*liberman, 1968*). Other medications such as ipratropium bromide and Albuterol by their action on muscles, increasing the size of small airways. In complicated cases when the patients suffer from difficulty in breathing, mechanical breathing support by wearing special mask at night is require to push air into lungs. Bi-level positive airway pressure (BiAPP) ventilator is a mechanical breathing support function to provide blood with adequate amount of oxygen during sleep and improve sputum clearance when its used as a physical therapy (Moran F 2003).

3) Transplantation:

In severe cases when lungs of the individuals with CF seriously damage and exercise tolerance declined lung transplant become necessary, which in this case both lungs must be replaced because unreplaced lung might contain infectious bacteria and infect transplanted lung. In addition, liver and pancreas could be transplanted to alleviate liver disease and/or diabetes (*Fridell, 2005*). Lung transplantation is performed when other attempt such as mechanical device or antibiotic treatment for survival of patients is threatened (*Belkin, 2006*). In addition the patients must be enough healthy prior to transplantation to endure the procedure.

4) Gene therapy:

Autosomal recessive disease such as CF might be possible to treat by gene therapy through inserting a copy of normal DNA into the affected cells. Gene therapy procedure is not difficult invitro and

concept but in practice it has been proven quite difficult. First gene therapy attempt with adenovirus vector was unsuccessful due to low viral vectors efficiency immunogenicity to insert DNA into epithelial cells (*Crysta, 1994, Joseph, 2001 and Pickles, 2004*). Physiological correction of chloride movement in nasal epithelial cells from recombinant adeno associated viruses (AAV) serotype 2 CFTR gene therapy have shown by colleagues and Flotte even with low CFTR mRNA expression. Unfortunately repeated dose of aerosolised AAV CFTR treatment did not result in Spirometric value (*Moss, 2007*). In addition immunological response and toxicity to repeated administration of adenovirus vector still has concern (*Tosi, 2004*). CF gene therapy organization in the UK has worked to find alternative of adenovirus vector by developing non-viral vector for gene transfer (*Griesenbach, 2006*). They use cationic lipid vector in their gene therapy procedure in animal module and they got a best result and they believe that repeated dose of non-viral vector and new plasmid- and new way for delivering this vectors- would be developed in next few years (*Griesenbach, 2006*).

REFERENCES

- Assael, BM; Castellani C, Ocampo MB et al. (September 2002). "Epidemiology and survival analysis of cystic fibrosis in an area of intense neonatal screening over 30 years" (http:/ / aje. oxfordjournals. org/ cgi/ reprint/ 156/ 5/ 397). *American Journal of Epidemiology* 156 (5):
- 397–401. doi:10.1093/aje/kwf064. PMID 18718257. PMC 2569148. .

- Alves Cde A, Aguiar RA, Alves AC, Santana MA (April 2007). "Diabetes mellitus in patients with cystic fibrosis". *J Bras Pneumol* 33 (2): 213–21. PMID 17724542.

- Antonelli M, Midulla F, Tancredi G, et al.Bronchial artery embolization for the management of no massive haemoptysis in cystic
- Fibrosis. *Chest.* 2002; 121:796-801.

- American College of Obstetricians and Gynecologists and American College of Medical Genetics. *Preconception and prenatal carrier*
- *Screening for cystic fibrosis. Clinical and laboratory guidelines.* American College of Obstetricians and Gynecologists, Washington, DC, October 2001.

- Britton JR. Effects of social class, sex, and region of residence on age at death from cystic fibrosis. *BMJ* 1989;298:483-7.

- Blackman SM, Deering-Brose R, McWilliams R, *et al.* (October 2006). "Relative contribution of genetic and nongenetic modifiers to
- Intestinal obstruction in cystic fibrosis" (http:/ / linkinghub. elsevier. com/ retrieve/ pii/ S0016-5085(06)01659-3). *Gastroenterology* 131 (4):

- Bear CE, Li CH, Kartner N, Bridges RJ, Jensen TJ, Ramjeesingh M, Riordan JR. Purification and functional reconstitution of the cystic

- Fibrosis transmembrane conductance regulator (CFTR). Cell 1992; 68(4):809-818

- Belkin RA, Henig NR, Singer LG, *et al.* (March 2006). "Risk factors for death of patients with cystic fibrosis awaiting lung transplantation"
- (http:/ / www. pubmedcentral. nih. gov/ articlerender. fcgi? tool=pmcentrez& artid=2662949). *Am. J. Respir. Crit. Care Med.* 173 (6): 659–66.doi:10.1164/rccm.200410-1369OC. PMID 16387803. PMC 2662949.

- Collins FS. Cystic fibrosis: molecular biology and therapeutic implications.
- Science 1992; 256(5058):774-779.

- Cystic Fibrosis Foundation. Patient Registry 2007 Annual Report. September 2009. Available at http://www. cff.org/research/Clinical Research/PatientRegistryReport/. Accessed January 11, 2010.

- Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry2005 Annual Data Report. Bethesda: Cystic Fibrosis Foundation; 2006.

- Cheng SH, Gregory RJ, Marshall J, Paul S, Souza DW, White GA,et al. Defective intracellular traffic and processing of CFTR is the
- Molecular basis of most cystic fibrosis. Cell 1990; 63(4):827-834.

- Crystal RG, McElvaney NG, Rosenfeld MA, et al. Administrationof an adenovirus containing the human CFTR cDNA to the
- Respiratory tract of individuals with cystic fi brosis. *Nat Genet* 1994; 8: 42–51.

- Drumm ML, Konstan MW, Schluchter MD, et al. Geneticmodifi ers of lung disease in cystic fibrosis. *N Engl J Med* 2005;
- 353: 1443–53.

- De Lisle RC (September 2009). "Pass the bicarb: the importance of HCO3- for mucin release" (http:/ / www. PubMed central. nih. gov/
- articlerender. Fcgi? Tool=pmcentrez& artid=2735941). *J. Clin. Invest.* 119 (9): 2535–7. Doi: 10.1172/JCI40598. PMID 19726878.
- PMC 2735941

- Davies JC, Alton EW, Bush A (December 2007). "Cystic fibrosis" (http:/ / www. PubMed central. nih. gov/ articlerender.
- Fcgi? Tool=pmcentrez& artid=2137053). *BMJ* 335 (7632): 1255–9. doi:10.1136/bmj.39391.713229.AD. PMID 18079549. PMC 2137053

- Davis LB, Champion SJ, Fair SO, Baker VL, Garber AM (April 2010). "A cost-benefit analysis of preimplantation genetic diagnosis for
- Carrier couples of cystic fibrosis". *Fertil. Steril.* 93 (6): 1793–804. doi:10.1016/j.fertnstert.2008.12.053. PMID 19439290.

- Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947-2003. *Eur Respir J* 2007; 29:522-6.
- Elborn JS, Shale DJ, Britton JR. Cystic fibrosis: current survival and population estimates to the year 2000. *Thorax* 1991; 46:881-5.
- Elias S, Annas GJ, Simpson JL (April 1991). "Carrier screening for cystic fibrosis: implications for obstetric and gynaecologic practice". *Am. J. Obstet. Gynecol.* 164 (4): 1077–83. PMID 2014829.
- Elphick H, Southern K. Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. *Cochrane*
- Farrell PM, Lai HJ, Li Z, Kosorok MR, Laxova A, Green CG, et al. Evidence on improved outcomes with early diagnosis of cystic fibrosis through neonatal screening: enough is enough! *J Pediatr* 2005; 147(suppl 3):S30-6.
- Freudenheim, Milt (2009-12-22). "Tool in Cystic Fibrosis Fight: A Registry" (http:/ / www. nytimes. com/ 2009/ 12/ 22/ health/ 22cyst. html? 8dpc=& pagewanted=all). *New York Times*: pp. D1. . Retrieved 2009-12-21.
- Fridell JA, Vianna R, Kwo PY, *et al.* (October 2005). "Simultaneous liver and pancreas transplantation in patients with cystic fibrosis". *Transplant. Proc.* 37 (8): 3567–9.
- doi:10.1016/j.transproceed.2005.09.091. PMID 16298663
- Gilljam M, Antoniou M, Shin J, Dupuis A, Corey M, Tullis DE (July 2000). "Pregnancy in cystic fibrosis. Fetal and maternal outcome". *Chest* 118 (1): 85–91. doi:10.1378/chest.118.1.85. PMID 10893364.
- Govan JRW, Glass S. The microbiology and therapy of cystic fibrosis lung infections. Rev Med Microbial 1990; 1:19–28.
- Griesenbach U, Geddes DM, Alton EW. Gene therapy progress and prospects: cystic fi brosis. *Gene Ther* 2006; 13: 1061–67.
- Hart N, Polkey MI, Clement A, et al.Changes in pulmonary mechanics with increasing disease severity in children and young adults with cystic fibrosis. *Am J Respir Crit Care Med.* 2002; 166:61-66.
- Hardin DS (August 2004). "GH improves growth and clinical status in children with cystic fibrosis -- a review of published studies" (http:/ /eje-online. org/ cgi/ pmidlookup?view=long& pmid=15339250). *Eur. J. Endocrinol.* 151 Suppl 1: S81–5. PMID 15339250. .
- Hansen CR, Pressler T, Koch C, Hoiby N (March 2005). "Long-term azitromycin treatment of cystic fibrosis patients with chronic Pseudomonas aeruginosa infection; an observational cohort study". *J. Cyst. Fibrosis.* 4 (1): 35–40. doi:10.1016/j.jcf.2004.09.001. PMID 15752679.
- Haworth CS, Selby PL, Webb AK, *et al.* (November 1999). "Low bone mineral density in adults with cystic fibrosis" (http:/ / www.

pubmedcentral. nih. gov/ articlerender. fcgi? tool=pmcentrez& artid=1745400). *Thorax* 54 (11): 961–7. doi:10.1136/thx.54.11.961.

- PMID 10525552. PMC 1745400.

- Joseph PM, O'Sullivan BP, Lapey A, et al. Aerosol and lobar administration of a recombinant adenovirus to individuals with cystic fibrosis. I. Methods, safety, and clinical implications. *Hum Gene Ther* 2001; 12: 1369–82.

- Kuver R, Lee SP (April 2006). "Hypertonic saline for cystic fibrosis". *N. Engl. J. Med.* 354 (17): 1848–51; author reply 1848–51.doi:10.1056/NEJMc060351. PMID 16642591

- Lieberman J (July 1968). "Dornase aerosol effect on sputum viscosity in cases of cystic fibrosis". *JAMA* 205 (5): 312–3. doi:10.1001/jama.205.5.312. PMID 5694947.

- McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB (November 2008). "Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis" (http:/ / www. pubmedcentral. nih. gov/ articlerender. fcgi? tool=pmcentrez&artid=2577727). *Am. J. Respir. Crit. Care Med.* 178 (9): 921–8. doi: 10.1164/rccm.200712-1804OC. PMID 18658109. PMC 2577727.

- Marchand E, Verellen-Dumoulin C,Mairesse M, et al. Frequency of cystic fibrosismembrane conductance regulator gene mutations and 5T allele in patients withallergic bronchopulmonary aspergillosis.*Chest.* 2001; 119:762-767.

- McCallum TJ, Milunsky JM, Cunningham DL, Harris DH, Maher TA, Oates RD (October 2000). "Fertility in men with cystic fibrosis: an update on current surgical practices and outcomes". *Chest* 118 (4): 1059–62. doi:10.1378/chest.118.4.1059. PMID 11035677.

- Merelle ME, Schouten JP, Gerritsen J, Dankert-Roelse JE. Influence of neonatal screening and centralized treatment on long-term clinical outcome and survival of CF patients. *Eur Respir J* 2001; 18:306-15.

- Mitchell, Richard Sheppard; Kumar, Vinay; Robbins, Stanley L.; Abbas, Abul K.; Fausto, Nelson (2007). *Robbins basic pathology*. Saunders/Elsevier. ISBN 1-4160-2973-7.

- Moran A, Hardin D, Rodman D, et al. Diagnosis, screening and management of cystic fibrosis related diabetes mellitus: a consensus conference report. *Diabetes Res Clin Pract.*1999; 45:61-73.

- Minarowski Ł, Sands D, Minarowska A, Karwowska A, Sulewska A, Gacko M, Chyczewska E. Thiocyanate concentration in saliva of cystic fibrosis patients. Folia Histochem Cytobiol. 2008; 46(2):245-6. http:/ / versita. Metapress. Com/ content/ 12805r021413m867/.

- Moran F, Bradley J (2003). "Non-invasive ventilation for cystic fibrosis". *Cochrane Database Syst Rev* (2): CD002769. doi:10.1002/14651858.CD002769. PMID 12804435.

- Moss RB, Milla C, Colombo J, et al. Repeated aerosolized AAV-CFTR for treatment of cystic fi brosis: a randomized placebo-controlled phase 2B trial. *Hum Gene Ther* 2007; 18: 726–32.
- O'Malley CA (May 2009). "Infection control in cystic fibrosis: cohorting, cross-contamination, and the respiratory therapist" (http:/ / www. rcjournal. com/ contents/ 05. 09/ 05. 09. 0641. pdf). *Respir Care* 54 (5): 641–57. doi: 10.4187/aarc0446. PMID 19393108. .
- Okiyoneda T, Lukacs GL. Cell surface dynamics of CFTR: the ins and outs. Biochim Biophys Acta 2007; 1773(4):476-479.
- Pai VB, Nahata MC (October 2001). "Efficacy and safety of aerosolized tobramycin in cystic
- fibrosis". *Pediatr. Pulmonol.* 32 (4): 314–27. doi:10.1002/ppul.1125. PMID 11568993
- Pickles RJ. Physical and biological barriers to viral vector-mediated delivery of genes to the airway epithelium. *Proc Am Thorac Soc* 2004; 1: 302–08.
- Quinton PM (June 2007). "Cystic fibrosis: lessons from the sweat gland" (http:/ / nips. physiology. org/ cgi/ pmidlookup? view=long&pmid=17557942). *Physiology (Bethesda)* 22: 212–25. doi:10.1152/physiol.00041.2006. PMID 17557942. .
- Quinton PM. The neglected ion: HCO3-. Nat Med 2001; 7(3):292-293.
- Ratjen F. New pulmonary therapies for cystic fibrosis. Curr Opin Pulm Med 2007; 13(6):541-546.
- Ratjen FA (May 2009). "Cystic fibrosis: pathogenesis and future treatment strategies" (http:/ / www. rcjournal. com/ contents/ 05. 09/ 05. 09. 0595. Pdf). *Respir Care* 54 (5): 595–605. doi: 10.4187/aarc0427. PMID 19393104. .
- Ross LF (September 2008). "Newborn screening for cystic fibrosis: a lesson in public health disparities" (http:/ / www. pubmedcentral. nih. gov/ articlerender. fcgi? tool=pmcentrez& artid=2569148). *The Journal of Paediatrics* 153 (3): 308–13. doi:10.1016/j.jpeds.2008.04.061. PMID 18718257. PMC 2569148.
- Riordan JR, Rommens JM, Kerem BS, Alon N, Rozmahel R, GrzelczakZ, et al. Identification of the cystic fibrosis gene: cloning and
- Characterization of complementary DNA. Science 1989; 245(4922):1066-1073.
- Rommens JM, Iannuzzi MC, Kerem BS, Drumm ML, Melmer G,Dean M, et al. Identification of the cystic fibrosis gene: chromosome
- Walking and jumping. Science 1989; 245(4922):1059-1065.
- Reddy MM, Light MJ, Quinton PM. Activation of the epithelial Na_channel (ENaC) requires CFTR Cl– channel function. Nature 1999;
- 402(6759):301-304.
- Riordan JR. CFTR function and prospects for therapy. Annu Rev Biochem 2008; 77:701-726

- Schwiebert EM, Morales MM, Devidas S, Egan ME, Guggino WB.Chloride channel and chloride conductance regulator domains of
- CFTR, the cystic fibrosis transmembrane conductance regulator. Proc Natl Acad Sci USA 1998; 95(5):2674-89.

- Saadane A, Soltys J, Berger M. Role of IL-10deficiency in excessive nuclear factor–Kappa B activation and lung inflammation
- In cystic fibrosis transmembraneconductance regulator knockout mice.*J Allergy Clin Immunol.* 2005; 2:405-411.

- Stites SW, Plauatz MW, Bailey K, et al.Increased concentrations of iron and is oferritinsin the lower respiratory tract of
- Patients with stable cystic fibrosis. *Am JRespir Crit Care Med.* 1999; 160:796-801.

- Taussig LM, Landua LI, eds. *Pediatric Respiratory Medicine.* St Louis, Mo: CV Mosby Inc; 1999.

- Tabor A, Philip J, Madsen M, Bang J, Obel EB, Norgaard-Pedersen B (June 1986). "Randomised controlled trial of genetic amniocentesis in
- 4606 low-risk women". *Lancet* 1 (8493): 1287–93. PMID 2423826.

- Tan KH, Mulheran M, Knox AJ, Smyth AR (March 2003). "Aminoglycoside prescribing and surveillance in cystic fibrosis" (http:/ / ajrccm.
- atsjournals. Org/ cgi/ pmidlookup?view=long& pmid=12623858). *Am. J. Respir. Crit. Care Med.* 167 (6): 819–23.
- doi: 10.1164/rccm.200109-012CC. PMID 12623858.

- Van der Schans C, Prasad A, Main E (2000). "Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis". *Cochrane*
- *Database Syst Rev* (2): CD001401. doi:10.1002/14651858.CD001401. PMID 10796781.

- Wang X, Venable J, LaPointe P, Hutt DM, Koulov AV, Coppinger J, et al. Hsp90 cochaperone Aha1 downregulation rescues misfolding
- Of CFTR in cystic fibrosis. Cell 2006; 127(4):803-815.

- Westerman EM, Le Brun PP, Touw DJ, Frijlink HW, Heijerman HG (March 2004). "Effect of nebulized colistin sulphate and colistin
- Sulphomethate on lung function in patients with cystic fibrosis: a pilot study". *J. Cyst. Fibros.* 3 (1): 23–8. doi:10.1016/j.jcf.2003.12.005.
- PMID 15463883