

Cystic Fibrosis

What is cystic fibrosis?

Cystic fibrosis (CF), sometimes also named mucoviscidosis, is the most common fatal hereditary disease in Caucasians. It results from a defect in a single gene that makes a protein called cystic fibrosis trans-membrane conductance regulator (CFTR). This defect results in the secretion of thick, sticky mucus in the lungs and in the glands of the human body.

Almost all people with CF have nutrition problems and many go on to have liver damage and diabetes. In the lung, mucus coats the small airways, resulting in severe coughing, infection and eventual tissue damage.

Who does cystic fibrosis affect?

CF affects about 1 in 2,500 live births. Taking into account 5,0 million births in the European Union per year, the incidence of babies born with CF is around 2,000, making CF a significant health problem. Worldwide, approximately 70,000 individuals have CF; most are diagnosed by six months of age. Approximately one in 25 people of European descent is a carrier of a cystic fibrosis mutation.

CF is diagnosed in boys and girls equally. For unclear reasons, males tend to have a longer life expectancy than females. Life expectancy depends largely upon access to health care. In 1959, the median age of survival of children with CF was six months. Life expectancy in developed countries for infants born in 2006 with CF is around 37 years. However, the life expectancy in developing countries is much less: the majority of patients do not live past the age of ten.

Present treatments and shortcomings:

Lifelong daily physiotherapy is required to loosen mucus and ensure that the lungs remain clear. People with cystic fibrosis practice airway clearance techniques to get rid of the mucus. Some of these require help from family members, friends or therapists. One technique is called "postural drainage and percussion". Patients sit, stand or lie in a position that will help free up mucus as their chest and back are clapped.

Treatment of CF is designed to manage acute symptoms and to slow the progress of disease complications such as damage to the lungs and pancreas. It is optimised to the needs of each individual. Antibiotics are given both prophylactically and therapeutically against bacterial infections.

In addition, vitamins, nutritional support and pancreatic enzyme preparations are given to almost all people with CF. About one third of adults with CF take the enzyme rhDNase to thin the mucus in their lungs, and a similar number require medication to control their diabetes. Diabetes is typically treated with insulin injections or an insulin pump. Development of osteoporosis can be prevented by increased intake of vitamin

Cystic Fibrosis remains the most common fatal genetic disease in Europe. Advanced medical treatment has raised the average life span to 30 years. Treatments so far manage acute symptoms and slow the disease progression. Gene therapy may open the door for further progress.



D and calcium, and can be treated by bisphosphonates. Poor growth may be avoided through supplemental feeds or by administration of injected growth hormone.

Like those with emphysema and chronic obstructive pulmonary disease (COPD), CF patients often show a lack of the protein alpha-1-antitrypsin (AAT) in the lung and this is thought to contribute to the development of chronic lung damage. An inhaled form of AAT has been developed which has shown to be effective in stabilising lung function and reducing the number of acute exacerbations.

What's in the development pipeline?

In 1995, results of a four-year, double-blind, clinical trial supported by the Cystic Fibrosis Foundation were published. The study design consisted of treating CF patients with a non-steroidal anti-inflammatory drug (NSAID). Researchers were able to demonstrate that the compound slowed the rate of pulmonary decline over a four-year period. Those taking the medication had better growth and were in the hospital less frequently than those who did not. The effect on pulmonary function took years to show.

In 2007, researchers confirmed that patients with CF who took an NSAID twice daily over a period of two to seven years had a 29 percent reduction in loss of lung function compared to those who did not. The recent study included data on 1,365 CF patients who took the NSAID and 8,960 who did not, who were of similar age and disease severity.

Scientists believe that the lung damage that occurs in CF is due to inflammation, and that treatment with an anti-inflammatory drug will presumably decrease inflammation in the lung, thereby slowing damage. So far, this therapeutic approach has not yet been authorised for general use.

Antibiotics are key tools in the management of cystic fibrosis. The combination of a compound for intravenous infusion and an inhalation antibiotic has been found to be particularly effective against the *Pseudomonas aeruginosa* bacterium that infects about half of all people with CF and which often develops multiple antibiotic resistances. Developing new antibiotics is essential to keep ahead of emerging resistance, and there is a liposomal nebulized monobactam for inhalation in development.

A major step forward was the announcement in August 2000, when scientists made it public that they had completely sequenced the *Pseudomonas* genome, an important tool for developing new therapies to combat this deadly pathogen. An alternative approach is the development of a new vaccine against *Pseudomonas* that is based on specific protein components of the bacterium.

Researchers are developing transgenic Bile Salt Stimulated Lipase (tgBSSL) as an alternative to existing pancreatic enzyme preparations.

A particularly interesting new approach to CF therapy is the development of a small molecule protein repair agent called CPX, which has the ability to bind to the defective CFTR protein in the epithelial cells of the lungs of CF patients and improve its functioning there, counteracting the build-up of mucus. This compound is currently in Phase 3 clinical trial.

In some patients, CF is caused by a non-sense mutation (also known as premature stop codon) in the gene that makes the CFTR protein. A new compound has been shown to partially restore CFTR production in animals with CF due to a non-sense mutation. Phase 1 trials in patients are underway to understand whether this molecule can safely increase functional CFTR protein in the cells of such patients.

Much research has been devoted to developing new treatments to help thin and clear the thick mucus that fills the airways in CF. Mucus thickness depends on sodium, chloride and water secretion from the cells lining the airways.

Such new treatment principles include a molecule which blocks mucus over-production, a purine nucleotide receptor type 2 stimulating compound, a ClC-2 chloride channel-opener, a compound which facilitates mucus clearance, a molecule that activates an alternative salt channel and an inhibitor of the sodium ion channel which increases water excretion.

The longer-term future:

CF has been seen as an ideal test for gene therapy, since restoration of a normal version of the CFTR gene into epithelial cells of the lung and digestive system would remedy the underlying defect in CF, with the prospect of curing it. However, although the feasibility of this approach has been demonstrated by researchers, two major problems remain:

Firstly, the efficiency of gene transfer has been too low to create significant clinical benefit and, secondly, the expression of the transferred gene has been very short-lived, i.e. only one to two weeks. Both liposomes and genetically manipulated viruses have been used as vectors for gene insertion, but it seems likely that much more fundamental research will be needed before this approach can be considered a real therapeutic alternative.



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Last update: June 2008