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# CYSTIC FIBROSIS

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**Summary**

Cystic fibrosis is the most common autosomal recessive genetic disease that limits lifespan in white populations. Hundreds of mutations have been discovered, with a huge range of clinical expressions. Identification of subjects with cystic fibrosis and carriers of the mutation enables genetic counseling and disease prevention. Early diagnosis, nowadays often through neonatal screening, allows early multidisciplinary approach with a positive impact on longevity and an increasing number of adult patients. As more patients live longer, the epidemiological indicators change and the number of complications on different organs increase.

Standardization of care in cystic fibrosis centers with continuous multidisciplinary and longitudinal follow-up from pediatric age to adulthood contributes largely to better control of the disease and improving the quality of life.

***Keywords:*** cystic fibrosis; pathogenesis; disease presentation; diagnosis, treatment.

Cystic fibrosis (CF) is a hereditary disorder with autosomal recessive inheritance affecting many organs, primarily the respiratory system, the digestive tract and the reproductive system [1]. The first disease description dates seventy years ago, when patients died mostly in infancy due to severe malabsorption and diarrhea [2]. Life-expectancy of patients born nowadays is 50 years of longer [3,4]. Patients' outcome is determinated by the course of lung disease that is the main cause of a shortened life-span.

The disease incidence is approximately 1 in every 3,200 live births in northern and western Europe and USA, 1 in 15,000 African-American births and 1 in 32,000 Asian-American births [5]. Cystic fibrosis is caused by mutations in a single gene colloquially called the CF gene that encodes the *cystic fibrosis transmembrane conductance regulator* (CFTR) protein [6]. Abnormal chloride conductance in apical membra-

nes of epithelial cells lining the airways, pancreatic ducts, sweat ducts, intestines, biliary tree, and vas deferens results in impaired ion composition of secretions that becomes dehydrated and viscous; therefore the alternative name for the disease – *mucoviscidosis*. The consequence of liquid depletion in secretions is mucus obstruction leading to fibrotic and cystic deformations and finally tissue destruction [4]. It is worth mentioning that CFTR has other regulatory functions besides chloride transport. By now around 2000 mutations of the CFTR-gene have been described, but the functional importance of many is not known. The mutation F508del is found in approximately 70% of CF patients in northwestern Europe and USA.

Within the last decades the life span of CF patients has been notably prolonged, thanks to the development of new therapeutical approaches and interventions with impact on the disease course. Some important interventions are: disease detection through neonatal screening [7], aggressive nutritional support [8], and new treatments for lung inflammation, infection and mucocilliary clearance [9,10,11]. Further progress came with exciting new treatments aiming to treat causes rather than just symptoms, i.e. mutation-specific therapies allowing read-through of premature stop codons, CFTR potentiators and CFTR correctors [12,13]. Nowadays lung transplantation is a treatment option for end-stage lung disease [14]. Specialized CF centers with a multidisciplinary team have a crucial, central role in developing and implementing new therapies based on understanding the underlying pathophysiology of the disease [15].

Despite of well known diagnostic algorithms for classic and non-classic CF [16], CF is not always a straightforward diagnosis. There is a small subset of patients, often adults, who have atypical clinical manifestations [17,18]. Classic CF presentation includes pancreatic insufficiency, malnutrition, chronic lung disease and in postpubertal males obstructive azoospermia. The diagnosis is usually suspected within the first years of life and easily confirmed. On the contrary, patients with atypical presentations are often pancreatic sufficient and have mild clinical symptoms. The diagnosis is delayed to adolescence or adulthood, sometimes with the burden of equivocal results of diagnostic tests.

Special challenge present patients that might have CF, but they do not meet classic diagnostic criteria for CF, i.e. those having intermediary or normal concentrations of chloride in the sweat, those carrying only one mutation or those with a monosymptomatic phenotype. These patients are referred to as having a CFTR-related disease. It is important to differentiate them from CF patients, for psychological and practical reasons, because they have much better prospects [19,20].

The clinical syndrome we recognize as CF has considerable variability, and at least some of this variability seems to be associated with specific gene mutations.

However, individuals with the same genotype can differ considerably, i.e. regarding the severity of lung disease. This can be explained by the influence of other intrinsic factors like gene modifiers and extrinsic factors such as life-style, environmental influences, treatment choices etc. [21]. Therefore one should be extremely careful when predicting the disease severity and patient's prognosis merely on the genotype.

With the prolonged life expectancy of CF patients, especially those born in this millennium, there are societies with a bigger proportion of adult patients than children. In Canada the median age of survival has increased from 37.3 years in 2002 to 47.7 years in 2012. [4]. The proportion of adult patients in Croatia is constantly increasing in the past two decades as well; they are 1/5 of all registered patients [22].

**Patophysiology**

Most studies regarding how CFTR dysfunction leads to the phenotypic disease were performed on epithelial cells of CF airway samples. Bulk of evidence suggests that the main features are diminished chloride efflux to the lumen and excess sodium and water reabsorption, leading to dehydration of airway surface materials. Airway surface liquid depletion is thought to impair mucociliary clearance. Thus, the viscous mucus accumulates obstructing the airways and phlegm harbors pathogenic bacteria. The clinical consequence is persistent cough and bronchitis, often accompanied with broncho-obstruction – the earliest clinical signs of impaired lung function in CF.

With time, mucus on the epithelium forms plaques with anaerobic niches that can bind opportunistic bacterial pathogens. Characteristically, *Pseudomonas aeruginosa* over time adjusts to this media, synthesizes an alginate coat and forms biofilms that are very difficult to clear with standard antibiotic treatment. The consequence of this is a vicious circle of phlegm retention, infection and chronic neutrophil inflammation that perpetuates itself [5,9,23].

Many patients develop a pronounced inflammatory reaction already in early age, prior to infections. This is believed to be a direct effect of CFTR dysfunction leading to dysregulated host inflammatory response. In any case, a strong and constant neutrophilic airway inflammation enhanced with chronic infection and other inflammatory stimuli is a milestone of CF airway disease [5,9].

Impaired electrolyte conductance contributes to an impaired bioelectric potential difference (PD) across the epithelial membrane. The PD can be measured *in vivo* in the nasal epithelium and *in vitro* in rectal biopsies. Assessing basal PD and changes in response to various stimuli is used as a diagnostic tool in doubtful cases and in research laboratories to test the effectiveness of new drugs for CF [5,9].

The pathophysilogy of changes within the pancreas are similar to those in the airways: dysfunctional CFTR gene leads to lack of chloride secretion in pancreatic ducts and as a consequence reduced chloride/bicarbonate exchange, resulting in a smaller volume of pancreatic juices that is rich in proteins and poor in bicarbonates. These alterations are responsible for obstruction and autodigestion of the pancreas that starts early in embryonic life, causing exocrine pancreatic insufficiency at birth or within the first months or years of life [24].

Impaired ion conductance exists in bile ducts and in *vas deferens* as well; viscous secretions obstruct the canals and lead to reactive inflammation and finally fibrotic degeneration [25].

In contrast to epithelial cells, the functioning CFTR protein in sweat glands enables reabsorption of salt and water from the sweat. Therefore the sweat concentration of chloride and sodium is increased in CF and this is the main laboratory test to diagnose the disease. Only a small proportion of patients (1- 2%) with some rare mutations have normal sweat electrolyte concentrations [26].

**Clinical features**

*Lung disease* is present in virtually all CF patients and is the determining factor of survival. Some patients experience early respiratory symptoms in infancy with nonproductive, exhausting cough. Symptoms mimic bronchiolitis with obstructive dyspnea and wheezing. However, the lung disease may evolve gradually, in months and even years, presenting as chronic broncho-obstruction, bronchitis, recurrent pneumonias and hyperinflation of the lung parenchyma. As the disease progresses, peribronchal fibrosis, athelectasis and bronchiectasis develop. Attributes of chronic lung disease are chronic respiratory insufficiency and *cor pulmonale* [8,23].

In addition to chronic lung disease patients experience pulmonary exacerbations, sometimes pneumothorax in the advanced disease. In adolescents and adults (rarely in children) one should consider *allergic bronchopulmonary aspergillosis* in refractory exacerbations.

Initialy, the pathogens causing lung infection are common microorganisms for the age of the child (viruses, *Haemophylus* and *Pneumococcus* strains). Later, usual isolates are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Burkholderia cepacia*. Pseudomonas infections are difficult to eradicate due to its' capacity to transform and form biofilms [26].

Chronic pancreatic insufficiency is present in 85% of the CF population. Lack of exocrine pancreatic secretion leads to maldigestion and secondary malabsorption, steatorrhoea and increased intestinal nitrogen loss [24]. Malnutrition, specifically

long-lasting energy deficiency, has a negative impact on the respiratory system, enhancing the number of lung infections and degree of inflammation that favor structural changes in the airways [24,26].

Endocrine function of Langerhans islets is usually maintained until adolescence and adulthood. Finally about one third of patients develop *cystic fibrosis related diabetes* (CFRD), a unique form of diabetes that has characteristics of type I and type II diabetes [27].

Neonates with CF can present with transient *cholestatc jaundice* caused by obstruction of intrahepatic bile ducts. Older patients are at risk for *focal billiary cirrhosis*, but clinically apparent liver disease occurs in only a small portion of patients and usually presents by 15 years of age. Liver failure is the second leading cause of death in CF [26].

Neonates can also present with *meconium ileus*. Older children and adults can develop *distal obstructive syndrome (DIOS)*, a syndrome of partial or complete postneonatal distal small bowel obstruction caused by stool plugs, also known as meconium ileus equivalent [5,9].

As a consequence of the chronic inflammation, hypomotility, recurrent infections and frequent antibiotic use CF patients can develop *small bowel bacterial overgrowth syndrome*, one of the factors contributing to malabsorption and malnutrition [28].

Excessive loss of sodium and chloride through sweating sometimes causes *hyponatriemic dehydration* and *hypochloremic metabolic alkalosis*. This metabolic imbalance can be the presenting symptom in early infancy [29].

Growth and thriving largely depends on adequate substitution of pancreatic enzymes and hypercaloric nutrition. Often, puberty is delayed for one or two years due to impaired growth and maturation [29].

Most male patients (98%) are azoospermic and unfertile due to vas deferens obstruction, with normal other reproductive functions. Women are fertile, although they may experience difficulties in getting pregnant due to dehydrated cervical secretions [30].

## Diagnosis

CF is primarily a clinical diagnosis. It should be suspected in any child who demonstrates typical clinical features of CF or who was born to a family with a known history of CF or has a positive newborn screening. Suspicion is followed by laboratory testing to prove CFTR dysfunction. This includes either measuring sweat chloride concentration, or genetic testing, or measurement of the nasal PD [31]. The sweat test is the long-standing standard and mostly used to confirm CF. Mutation

identification is not obligatory for the diagnosis in patients with clinical symptoms and elevated sweat chlorides. However, knowing the mutations is relevant for family genetic counseling and important because some mutations can be corrected with the new therapies.

*Neonatal screening* has been implemented in many countries. This allows disease detection in the pre-symptomatic phase. Early implementation of various therapeutical procedures should provide better disease control; ensure optimal nutritional status and altogether better prognosis [7].

**Treatment options**

CF treatment consists of life-lasting measures to control symptoms and disease progression, as there is still no causative therapy [9]. However, alternative drug treatment that affects intercellular function, like trafficking, expression or function of CFTR has emerged. One of these mutation specific treatments is registered for use in 2012.y: a CFTR potentiator *ivacafor* (Kalydeco) for patients with G551D mutation. In progress and with promising results are studies with a corrector compound (VX809, *lumakaftor*) and a drug that induces read-through of premature stop codons in class I mutations (PTC124-*ataluren*). Some more substances targeting different ways of correcting the CFTR function or biochemical aberrations of CF are under investigation [32].

While waiting for therapies that treat the basic defect, the milestone of CF therapy remains *symptomatic treatment*. It is mostly focused on respiratory and gastrointestinal symptoms with nutritional support.

Respiratory treatment is focused on managing infection, inflammation and improving airway clearance, and, for end stage lung disease, lung transplantation (9).

**Infections**. Aggressive antibiotic therapy was one of the main contributors to longer survival of CF patients. Patients move from phases of rather stable lung disease with occasional exacerbations to the state of chronic infection. In each phase antibiotic treatment plays an important role. Antibiotics can be given intravenously, orally and in inhalations. Nowadays inhaled antibiotics (tobramycin, colistin, aztreonam) are the treatment choice for both early *Pseudeomonas* eradication and control of chronic colonization [26,33,34].

**Inflammation**. Neutrophil-dominated inflammation in the airways is a hallmark of CF. Although the mechanism leading to pronounced inflammation is not well understood, inflammation contributes to lung damage and disease severity. *Oral corticosteroids* yield improvement in lung function and reduce pulmonary exacerbations, but their use is highly limited due to unacceptable adverse event profile.

Unfortunately, *inhaled corticosteroids* have no proven effect on the course of CF lung disease and are not recommended unless marked bronchial hyper-reactivity is present.

High dose *oral* i*buprofen* was shown to be effective in slowing the decline in $FEV_1$, but it is not an accepted treatment in all centers [5,35].

*Macrolide* antibiotics have received attention in CF because of their remarkable effect in patients with diffuse panbronchiolitis. Azitrhomycin is nowadays recognized and advised as an immunomodulatory agent for CF, but the exact mechanism of action remains unclear.

**Mucolytic therapy**. Airway surface liquid depletion and viscid airway secretions are also a hallmark of CF. Mucolytics such as *N-acetylcysteine* have little effect on lung disease in these patients. On the contrary, inhaled *donorase-alfa* (recombinant human DNAse) effectively reduces sputum viscosity and number of exacerbations, and improves lung function in patients with mild to modest lung disease [36].

Short –term *hypertonic saline solution* improves lung function in CF patients, but long-term effects have to be yet proven. Inhaled *powdered mannitol* (Bronchitol, Ardiol) is an alternative and acceptable mucolytic [36].

**Lung transplantation**. This is the final therapeutic option for end-stage lung disease. In the past decades the procedure itself and post-transplant care have improved substantially [37]. The best timing and selection of candidates for transplantation are still a matter of dispute. It is important to recognize that lung transplantation is not a cure for CF patients, but represents a transfer to a new health-state in wich all other manifestations of CF persist and may worsen.

**Airway clearance techniques.** Chest physical treatment is an inevitable part of CF care. There are many techniques: simple percussion, different methods aiming to provoke coughing, high frequency chest wall oscillatory drainage, autogenic drainage etc. The choice depends on technical availability, competence of the staff, age and preferences of the patient.

Active **immunization** is an important issue. Patients should follow the national program. No consensus has been reached about extra immunization so far, but there are sugestions that vaccination against pneumoccocus, chickenpox, the flu and hepatitis A are beneficial [38].

**Gastrointestinal system and nutrition**. With longer survival of CF patients the numbers of gastrointestinal complications increase. Therefore collaboration with other specialists like gastroenterologists, endocrinologists, dietitians etc. is an imperative.

Nutritional therapy is based on three main components: pancreatic enzyme replacement, vitamin supplementation and quantitatively and qualitatively balanced diet ensuring at least 20% more calories than the RDA values in order to meet raised

energy demands caused by the hypermetabolic state [39]. Patients with CF and poor nutritional status are more prone to lung infections and earlier decline in $FEV_1$, so gastroenterological therapy must be included in everyday care.

## Conclusion

When CF is suspected in the presence of typical clinical features it must be confirmed by laboratory testing. The awareness of doctors to recognize the symptoms, especially pediatricians who see patients at an early age is crucial for detecting the disease, therefore competence should be worked on.

Neonatal screening enables detecting the disease in asymptomatic individuals. However, it raises some controversies and new challenges regarding treatment and prevention of complications. Main determinants of CF outcome is early detection and good control of pulmonary disease, that can be achieved through multidisciplinary treatment including a pulmonologists, gastroenterologists, dietitians and other specialties. With better care and longer lifespan of many patients we are witnessing a dramatic increase in the proportion of adult patients, in some countries surpassing the pediatric population. This brings new challenges, especially for doctors in adult medicine who face some new and less known CF presentations emerging during the life course.

It is now well established that best care for CF patients is provided in specialized CF centers that ensure multidisciplinary and longitudinal follow-ups of patients from infancy to adulthood, taking in consideration special needs and difficulties in translation from pediatric to adult CF units. Based on European experiences and published recommendations for standards of care, it is imperative to reorganize medical care for CF patients in Croatia, where already one fifth patients are adults [22].

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Sažetak

## Cistična fibroza

Cistična fibroza je najčešća nasljedna, autosomalno recesivna bolest koja utječe na dužinu života u bijeloj rasi. Danas je prepoznato više stotina mutacija uz veliku varijaciju ekspresije bolesti. Prepoznavanje bolesnika i nosilaca mutacije pruža mogućnost genskog savjetovanja i prevencije bolesti. Rano dijagnosticiranje, sve češće pomoću neonatalog probira, omogućuje rani multidisciplinarni terapijski pristup uz značajno produljenje životnog vijeka i sve većeg broja odraslih bolesnika. Dužinom životnog vijeka mijenjaju se epidemiološki pokazatelji bolesti te se uočava sve više komplikacija bolesti na drugim organskim sistemima.

Osnivanje specijaliziranih centara za liječenje cistične fibroze s multidisciplinarnom longitudinalnom skrbi za bolesnike od pedijatrijske do odrasle dobi predstavlja daljnji doprinos kontroli bolesti i kvalitete života bolesnika.

***Ključne riječi:*** cistična fibroza; patogeneza; klinička slika; dijagnostika; liječenje.

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