http://doi.org/10.17638/03150606

Does Cystic Fibrosis Increase the Risk of Severe COVID-19 Infection?

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Cystic fibrosis is a condition that commonly affects the airways, whereby patients produce thick mucus that can lead to swelling and infection. It is caused by changes in a particular gene called CFTR and sufferers have an average lifespan of around 40 years. Following the recent COVID-19 pandemic, the question of whether people with cystic fibrosis are at a higher risk has been studied by the medical community since coronavirus also affects the airways. People with cystic fibrosis who caught coronavirus were found to have improved outcomes compared to people without cystic fibrosis. However, two problems common to patients with cystic fibrosis were seen to worsen outcomes, although they are not unique to cystic fibrosis. Research is still ongoing to determine how much of an impact COVID-19 has on those with cystic fibrosis.

Abstract

Cystic fibrosis (CF) is an autosomal recessive condition that results in misfolded or degraded cystic fibrosis transmembrane conductance regulator (CFTR) protein, which is commonly expressed in ciliated epithelial cells of the pulmonary and gastrointestinal tracts. This can have a range of cellular effects depending on the type of mutation, for example the disabling of chloride transport. The most common mutation is F508del, which activates the NF-κB pathway to initiate 'cytokine storms' that lead to inflammation and possible infection. Infection with COVID-19 also presents with respiratory symptoms and could be amplified by the 'cytokine storms' in CF patients. However, research suggests that CF patients infected with COVID-19 have a better prognosis than non-CF patients, potentially due to elevated levels of ATP. The severity of COVID-19 is reduced in CF patients compared to non-CF patients however, the disease severity has been shown to increase in those who have undergone solid organ transplant and have low lung function. Further research is still required to fully determine the mechanisms that reduce the risk of COVID-19 in CF patients.

Cystic fibrosis and COVID-19 severity

Cystic fibrosis (CF) presents as an accumulation of viscous mucus in the pulmonary and gastrointestinal tracts which can lead to, among other symptoms, inflammation and bacterial infections (Ratjen & Döring, 2003). The average life expectancy of sufferers is approximately 40 years, and the expression of the disease can vary considerably between patients (Dekkers *et al.,* 2013). CF is caused by an autosomal recessive mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene and is the most common autosomal recessive condition in Caucasian populations with an incidence rate of 1/3500 births (Mehta, Macek Jr., & Mehta, 2010). The CFTR gene encodes an epithelial chloride channel and its association with CF was first identified in 1989 through genetic linkage analysis, with positional cloning techniques locating the gene locus on the long arm of chromosome 7 (7q31) (Kerem *et al.,* 1989; Riordan *et al.,* 1989; Rommens *et al.,* 1989).

The global COVID-19 pandemic seemed to have little impact on CF patients based on a low number of early case reports (Colombo *et al.,* 2020; Ramos *et al.,* 2020). This came as a surprise to the CF community since other respiratory infections such as those caused by the influenza virus, can result in respiratory deterioration and death in CF patients (Viviani *et al.,* 2011). However, compromised lung function and solid organ transplant have since been associated with increased risk of severe COVID-19-related pneumonia or death, which has important implications for CF patients considering that CF is a major cause of lung transplantation (McClenaghan *et al.,* 2020; Naehrlich *et al.,* 2021). Therefore, understanding the genetic and molecular biology of CF in addition to its treatment is of great significance to medical researchers and healthcare professionals caring for high-risk CF patients during the COVID-19 pandemic.

The number of mutations found in the CFTR gene to date exceeds 2000, the most common of which is the F508del mutation (Cystic Fibrosis Mutation Database, 2011; De Boeck, 2020). Around 85% of global CF cases are associated with this mutation, which can be found in 90% of CF alleles (Rommens *et al,* 1989; Sarantis *et al,* 2020). The F508del mutation consists of a phenylalanine deletion at amino acid position 508 and results in protein misfolding, retention at the endoplasmic reticulum and subsequent degradation of the CFTR protein, preventing it from reaching its functional endpoint in the plasma membrane (Cheng *et al.,* 1990). The intracellular consequences of other CFTR mutations include impaired protein folding, production, gating, conductance, and splicing, as well as disrupted protein interactions (Riordan, 2008). The F508del mutation leads to the activation of nuclear factor kappa B (NF-κB), which is involved in immune and inflammatory responses (Salminen *et al,* 2008; Baltimore, 2009). NF-κB stimulates the release of interleukin 8 (IL-8) from bronchial epithelial cells which can cause rapid tissue degeneration and death if amplified by infection with the bacterium *Pseudomonas aeruginosa* (Bezzerri *et al,* 2011). NF-κB is trans-

Diagnosis of Cystic Fibrosis

Diagnosing CF is imperative in being able to apply effective treatment plans. The heel prick test involves taking a few drops of blood from a 5-day old new-born, allowing the detection of various conditions, including CF. Following a positive heel-prick test, the diagnosis is confirmed via a sweat test, which measures higher than normal concentrations of chloride in the neonates sweat, indicative of dysregulated chloride channels associated with CF. As the heel prick test was only developed in the UK in 2007 (Cystic Fibrosis Trust, 2021), previous screening methods involved a genetic test using the individual's blood or saliva, followed by the sweat test (NHS, 2021).

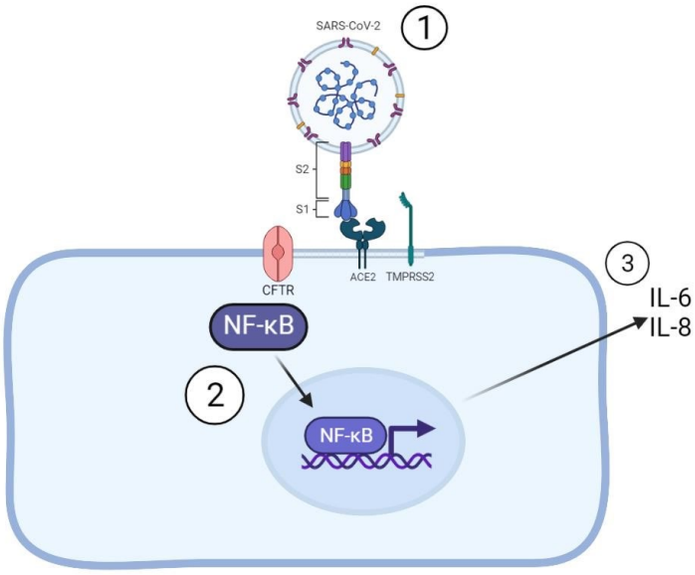

Figure 1. The cytokine storm in response to NF-κB activation in the presence of defective CFTR or its absence in response to SARS-CoV-2 infection. Virion binds to the ACE2 receptor and is translocated inside the cell by the TMPRSS2 enzyme. This triggers the migration of NF-κB inside the nucleus for transcription of cytokines and pro-inflammatory genes. Amplification of cytokines initiates the migration of neutrophils, leading to inflammation and subsequent damage to lung tissues.

located to the nucleus following an acute innate immune response and activates the transcription of pro-inflammatory genes and IL-8, triggering a 'cytokine storm' (Figure 1) (Kelly *et al,* 2013; Sarantis *et al,* 2020). Patients heterozygous for the CFTR gene possess a higher sensitivity to the NF-κB-mediated 'cytokine storms', which could be associated with an increased risk of vascular hyperpermeability, multiorgan failure, and death in response to COVID-19 infection due to their similar mechanisms of action (Jose & Manuel, 2020; Tay *et al,* 2020).

Management of cystic fibrosis

In order to control the condition, people living with CF need a mix of both lifestyle and medical management for the best possible results. The goal of management is preventing infections, reducing the accumulation of mucus in the lungs, treating other luminal mucus blockages, and providing the essential nutrition that sufferers lack due to malabsorption of nutrients. Due to the pancreatic insufficiency caused by the thickened mucus in CF, patients are given extra supplements, such as for fat soluble vitamins (Cystic Fibrosis Foundation, 2022). In regards to lifestyle, the recommendation is high calorie diets, exercise, keeping up with vaccines and flu jabs, and regular check-ups (NHS, 2021). Another essential method of managing symptoms is using airway clearance techniques taught by a physiotherapist to improve posture, ventilation, and continence (Daniels, 2010).

The medical treatment of CF is more complex as the combination of drugs differs depending on the type of mutation (Cystic Fibrosis Foundation, 2022). Some mutations are more responsive to certain treatments, while others are not. For example, the use of CFTR modulators was found to be very beneficial to those with the G551D mutation, but not as effective to those with F508 heterozygous or nonsense mutations (Pettit & Fellner, 2014). However, there are now studies and trials being conducted using combination therapies such as ivacaftor and tezacaftor that show promising results in their percent predicted forced expiratory volume in one second (ppFEV1), even for the F508del and nonsense mutation subgroups (Habib *et al.,* 2019).

Management of COVID-19 in patients with cystic fibrosis

Azithromycin is a bacteriostatic macrolide antibiotic regularly prescribed to CF patients that acts to prevent the growth of bacteria through its upregulation of type I and III interferons and genes involved in virus recognition (Cramer *et al.,* 2017; Colson *et al.,* 2020). It has been reported to have anti-viral properties that synergise with the effects of hydroxychloroquine *in vitro* (Bleyzac *et al.,* 2020; Ghazy *et al.,* 2020).

Initial investigations using this drug combination in COVID-19 patients was shown to virologically cure them (Gautret *et al.,* 2020). Another drug that is regularly administered to CF patients is dornase alfa, which has recently been linked to improved blood oxygenation in COVID-19 patients, although this has only been observed in a pilot study (Holliday *et al.,* 2021). It can be suggested, therefore, that either the antiviral action of azithromycin or the mucolytic effect of dornase alfa administered to CF patients (or both in conjunction) could be reducing the severity of COVID-19.

A common medical intervention for CF patients is lung transplantation. A trend has been observed between CF patients who have undergone solid organ transplant and more severe cases of COVID-19 (Mathew *et al.,* 2021). Although this trend is clearly seen across multiple CF populations, there is some contradiction between sets of data likely as a result of low population sizes.

COVID-19 affects the mucosal membranes lining the respiratory tract, resulting in respiratory inflammation, with severe cases resulting in an accumulation of fluid and debris in the lungs. Therefore, patients with other respiratory conditions such as asthma or chronic respiratory disease are considered 'vulnerable' to a more severe response to SARS-CoV-2 infection. Notably, those patients with COVID-19 and homozygous for a CFTR mutation have better prognosis. Abraham *et al.* (2021) hypothesized that this was due to elevated ATP levels in CF patients when compared to the normal population. This is further demonstrated by the studies conducted in 4 facilities in Oklahoma, USA. All participants started on a normal dose of 400 mg ATP supplement taken three to four times a day. This was increased if the patients tested positive for COVID-19. In all tests conducted across these facilities in 2020, there were virtually no recorded deaths attributed to COVID-19 after administration of ATP supplements. The majority that rejected the supplements died (Abraham *et al.,* 2021).

Summary and future directions

The mechanism of action of CF is widely acknowledged in the medical community, particularly that of the most common CFTR mutation; F508del. The condition affects the intestinal and respiratory epithelium, leading medical researchers to question if CF patients could be at higher risk during the COVID-19 pandemic, due to its impact on vulnerable patients in terms of disease severity. Both CF and COVID-19 infection impair the respiratory system and can lead to death in worst case scenarios. Surprisingly, the opposite was observed when CF patients infected with SARS-CoV-2 received a better prognosis than their non-CF counterparts (Abraham *et al.,* 2021). This is despite the fact that solid organ transplant and low lung function, which are common in CF patients, result in a more serious COVID-19 infection (Mathew *et al.,* 2021). Research is still ongoing to determine the risk of COVID-19 infection in people with CF, although the current evidence suggests that other factors could have greater impact.

We recommend further studies on whether COVID-19 severity remains low in CF patients experiencing 'long COVID-19' as there is little reference to the two in the scientific literature. Additional investigations into drug mechanisms in CF patients that could cause the observed reduction in COVID-19 severity will be necessary to analyse the importance of drugs such as azithromycin and dornase alfa in treating COVID-19. Currently, the population sizes for CF patients is limited due to their self-protective isolation requirements and the low incidence of the condition. Increasing population sizes will be necessary in establishing the significance of drug treatments in reducing COVID-19 severity in these patients. Comparisons between the severity of COVID-19 in CF patients with specific drug treatments (e.g. azithromycin, dornase alfa) and control groups of CF patients without these medications should be performed to determine their involvement in reducing disease severity or whether a cellular mechanism specific to CF is a cause. However, there are ethical considerations with removing certain medications from the treatment plan of CF patients such as the mucolytic dornase alfa, however there is a possibility that azithromycin can be replaced with a different antibiotic. This would need to be reviewed separately to outline the logistics of this line of research in a clinical setting and whether an *in vivo* animal model or in *vitro* study would be preferred.

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