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COVID-19 outcomes in people with cystic fibrosis

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Abstract

Purpose of review: The COVID-19 global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a dramatic impact that is still ongoing around the world. Cystic fibrosis (CF) has been identified as a possible risk factor of poor outcome.

Recent findings: Data collected by multiple National CF registries around the world have indicated that persons with CF (PwCF) are not more likely to be affected by SARS-CoV-2 than the general population. The course of SARS-CoV-2 is usually mild in PwCF who are relatively young. Severe outcomes have been described in patients with low lung function and in those with immune suppression (i.e. solid organ transplantation). Indirect impact of the pandemic on the CF community have also been observed, including difficulties in the organization of CF care, leading to a dramatic increase in telehealth for PwCF. The pandemic has further affected clinical research by complicating ongoing clinical trials. Vaccination appears important to all PwCF, with special priority on developing adequate vaccination scheme for transplant recipients. Long-term effects of COVID-19 on the CF population remains unknown.

Summary: The COVID-19 pandemic has caused significant impacts on PwCF and on healthcare professionals who provide specialized CF care and clinical research.

Keywords

SARS-CoV2; cystic fibrosis; pulmonary exacerbations; lung transplantation; clinical trials

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Introduction: the SARS-CoV-2 Pandemic

The COVID-19 global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a dramatic impact that is still ongoing around the world [1, 2]. Early reports out of Seattle, WA (one of the earliest outbreaks outside of China) noted high mortality in those admitted to the ICU – this work confirmed earlier cohort studies out of China and later outbreaks in New York City [3–5]. The clinical presentation of the disease presents in a wide spectrum from asymptomatic to severe respiratory failure and cardiovascular collapse with a high morbidity and mortality [6]. Additional manifestations of the disease can include disseminated intravascular coagulation, acute renal injury, gastrointestinal manifestations, cerebrovascular disease and neuropsychiatric problems [7]. Risk factors have included underlying respiratory disease, diabetes, obesity, ethnic and racial minorities and age, with increasing mortality with these key risk factors, especially age [8]. It is well documented that COVID-19 disproportionately affects disadvantaged communities such as Black, Latinx, Pacific Islander, and people with disabilities and chronic conditions [9]. Given the prevalence of respiratory disease and diabetes in CF, the COVID-19 pandemic has sent shock waves through the global CF community. Sheltering in place has become the norm with increasing isolation and an increased use of remote healthcare delivery to reduce spread of this infection in this vulnerable population [10–12].

Early experience with COVID-19 in the CF population

From the beginning of the COVID-19 pandemic, cystic fibrosis (CF) has been identified as a possible risk factor for SARS-CoV-2 infection and severe outcome **[13]. The fear of adverse outcomes in CF patients was related to previous experience with *influenza* virus infection, which is a known trigger of CF exacerbations and has previously resulted in respiratory deterioration and death in people with advanced CF lung disease [14]. As the healthcare systems around the world were put in major crisis mode by the COVID-19 pandemic, investigators underscored that CF patients with advanced lung disease have now improved prognosis and should not be denied access to intensive care units when they are affected by severe COVID-19 pneumonia [15].

Early experience on COVID-19 cases in persons with CF (PwCF) came from individual cases and small series of cases **[13, 16], often reporting a mild course of COVID-19. The small number of COVID-19 cases occurring in CF patients in areas of the world largely hit by the pandemic was surprising to the CF community. Although it was recognized that COVID-19 can be asymptomatic and not reported if patients were not tested for SARS-CoV-2 infection **[17], the apparent low rate of COVID-19 infection in CF patients was initially confirmed by the absence of SARS-CoV-2 identification by polymerase chain reaction (PCR) on respiratory samples in an Italian CF center [18] and by the very low prevalence of CF patients positive for SARS-CoV-2 serology in a cohort of Belgian patients with CF [19]. At that time, hypotheses for explaining these surprising findings included better compliance to social distancing and barrier measures in the well-trained CF population and/or the possible role of the widely prescribed antibiotic prophylaxis with azithromycin, which was believed to have some effects in the prevention of viral infections **[13]. Specificity of the CF lung immune environment have also been hypothesized to

play roles in the observed low prevalence and milder clinical presentation of COVID-19 in CF patients [20]. However, it was also noted that the situation was evolving fast and that close monitoring of CF cohorts will be necessary to fully establish the impact of COVID-19 **[13].

Large series of cases to monitor COVID 19 through national registries.

As the pandemic developed throughout the world, a number of countries began early tracking of COVID-19 cases in CF leveraging their respective National Registries. These efforts ensured that the CF community was given prompt information of the state of the pandemic in CF populations around the world. The first National report came from France, documenting 31 infected patients (confirmed by PCR or serology) from a population of approximately 7,500 in the first wave of the pandemic *[21]. Nineteen of the 31 patients were hospitalized some with critical care needs and 7 requiring supplemental oxygen **[17]. A later survey from Spain noted a reduced incidence of COVID-19 in CF with no deaths reported compared to the general population *[22]. Colombo et al. reported comparable findings from February to July 2020, noting 50% hospitalization and no deaths in the Italian population **[17].

From the start of the pandemic, a collaboration of National Registries (the Global Registry Harmonization Group) began a collaboration to track the pandemic globally in CF. The group of 8 countries, which rapidly grew to 21 countries, harmonized clinical variables and got consensus on case definitions and outcomes of interest **[16, 17, 23]. The cohorts now continue to grow – but key conclusions from these populations note that while COVID-19 incidence was lower than the relative incidence in the respective populations, severe cases and deaths were increasingly reported, and children presented with predominantly mild disease **[17, 23]. A follow-up study from the European CF Society Patient Registry noted that the case fatality rate was 3.85% (95% CI: 1.26–8.75); this was not found to be significantly different from the general population rate of 7.5% **[24]. The value of these collaborations has been to bring rapid clinical updates to the CF community and develop a process by which case definitions and outcomes can be standardized for reporting. More work is expected from the Global Registry Harmonization Group as countries track ongoing outbreaks of COVID-19 and longer term consequences of this pandemic on CF.

Risk factors for severe outcomes in CF patients

Although the course of COVID-19 is generally mild in CF patients, recent studies have reported a trend towards higher rates of hospitalization and intensive care unit care in CF patients compared to the age-matched general population **[24]. At least two major risk factors for severe outcomes have been identified in patients with CF: low lung function and solid organ transplantation. First, lower lung function has been associated with increased risk for hospitalization in CF patients infected by SARS-CoV-2 **[23]. Although this finding may reflect more severe outcome including the increased occurrence of respiratory failure due the lower lung function at baseline, it will require confirmation as it may also reflect a tendency to hospitalize patients with severe baseline lung disease, even though they show no sign of acute distress. Developing novel outcomes (e.g., the need for new

oxygen therapy and/or ICU care) will be useful to solve this question. Second, reports of poor COVID-19 outcomes (including ICU care and/or death) in individual cases or small series of CF patients living with lung transplantation have emerged early in the pandemic [25, 26]. As CF is one of the major causes for lung transplantation worldwide and a high proportion (for example, up to 20% in France) of adults with CF are living with a lung transplant, these findings were of major concern for the CF community. Studies involving multinational collaborations have confirmed that CF patients living with lung transplantation are at particular risk of severe COVID-19 related pneumonia and/or death **[16, 23, 24]. Of note, the risk of severe COVID-19 outcome in CF patients living with lung transplantation existed even in patients with normal lung function, suggesting that this risk is largely related to the immune suppressive drugs. Such finding is likely relevant to the smaller number of CF patients living with other solid organ transplant (e.g., liver or kidney), although their immune suppression regimen may be less potent.

Studies outside of the CF population have identified preexisting chronic illnesses as major risk factors of poor prognosis in patients affected by COVID-19 [27]. Among these, diabetes is present in 20 to 30% of CF patients and liver cirrhosis is found in 5 to 10% of CF patients. However, these factors have not been associated with severe COVID-19 related outcome in the CF population. A recent case of acute respiratory failure in a CF patient suggested that preexisting colonization with *B. cenocepacia* could be a risk factor for severe COVID-19 pneumonia, although this finding has not been reported in large registry studies [28].

Indirect consequences of COVID-19 on people with CF and specialized CF healthcare organization

The COVID-19 pandemic has had multiple indirect consequences on patients with CF. An unexpected, but positive, finding was the report of a reduced rates of CF exacerbations during the pandemic [29]. Such a finding, which has also been reported for other chronic respiratory diseases (e.g. chronic obstructive pulmonary disease [20]), could be related to a reduction in other viral infections, which are well-known triggers of CF exacerbations, due to social distancing and barrier measures. Lower access to healthcare system during the pandemic may have also contributed to a lower diagnosis of exacerbations.

CF patients also experienced indirect effects related to restrictive public policies in this pandemic time. For example, anxiety and depression are usually highly prevalent in CF patients and recent research suggest that psychological impact of daily life change at the time of COVID pandemic was high in the CF population [30, 31]. Recommended shielding against COVID-19 have been reported to result in low physical activity levels [32] and home-based physical exercise has been proposed to help minimizing indirect consequences of COVID-19 pandemic related restrictions [33].

As patients experienced difficulties to access CF centers and multiple restrictions were put on hospitals that where unable to provide usual CF care, patients and healthcare professional developed novel strategies to replace in person visit to centers, which resulted in rapid changes in the healthcare system organization **[34]. For example, the COVID-19 represented a unique opportunity to boost telemedicine programs. New

development included the implementation of novel systems for performing large-scale remote consultation with home spirometry [12, 35, 36], home collection of airway secretion samples for microbiology [10], and home management of diabetes based on teleconsultations [37]. There is little doubt that the experience gained during the pandemic will contribute to durable change in the CF healthcare model, although much work remains to be performed in integrating home monitoring in routine CF care.

Indirect effects of the COVID pandemic have also been observed for several activities related to CF care or research. First, the pandemic has resulted in difficulties in performing lung transplantation, especially during the lockdown periods [38, 39]. As lung transplantation offers a life saving opportunity for CF patients with advanced lung disease, this finding could have resulted in increased number of deaths without transplant (e.g., on transplant list). However, the concomitant release of elexacaftor-tezacaftor-ivacaftor, a highly effective CFTR modulator, just before the onset of the pandemic in multiple countries has likely limited the need for immediate transplant and prevented death in these patients [40]. Second, the pandemic has had a profound effect on clinical research, as reported by both the Cystic Fibrosis Foundation Therapeutics Development Network and the European Cystic Fibrosis Society clinical trials networks [41, 42]. Thus, the SARS-CoV-2 pandemic created multiple challenges for recruiting and following patients in clinical trials. These challenges were related in part to difficulties in the organization of research teams (e.g., in maintaining adequate research team, as nurses and doctors were involved in COVID acute care), but also in new COVID-related regulations that prevented patients to attend non-urgent hospital visits (e.g., during lockdown) or to perform procedures (e.g., spirometry, sputum induction) that are essential to CF clinical trials. Researchers developed novel strategies (e.g., home spirometry, electronic patient-reported outcomes, remote consenting and virtual study visits, procedures for shipment of biological samples) that contributed to reduce the negative impact of the COVID pandemic. Despite these efforts, the COVID pandemic has slowed CF research, which may have negative effects on patients with CF in the future.

Vaccination

The availability of a number of efficacious vaccines for COVID-19 appear to be curbing the COVID-19 pandemic (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines>). While up to date vaccination rates in CF have yet to be reported, introduction to vaccination have varied both regionally and nationally. To delineate the various approaches to vaccinations, Carr et al. reported how each of 21 different countries around the globe prioritized vaccine rollout [17]. At the time of this report, 15 of the 21 nations has started vaccination programs. Most of the countries had a prioritization approach that focused first on health care providers and the elderly and progressing to other risk groups however, the investigators found no uniform approach to the roll out of vaccines to persons with CF [43]. Vaccinations now has been expanded to adolescents in many developed nations – a key demographic in CF. Despite growing evidence that vaccines can have a profound impact on the spread of COVID-19 [29], it remains unclear the overall rate of acceptance of vaccines in persons with CF and how this could impact the population. Prior studies of influenza vaccinations note small proportions of persons with CF who do not

get annual recommended vaccinations [44]. An additional challenge to the CF community will be the equitable availability of vaccine to CF populations outside of Nations that pre-purchased vaccine [45].

An additional critical question that remains for the CF community is how to achieve appropriate levels of vaccination in persons with CF who are post-lung transplantation. This subgroup clearly has an increased risk of both severe disease and death with COVID-19 making successful vaccination critical to their care [16, 17, 23]. Recent reports suggest that immune response in lung transplant recipients is blunted even after two doses mRNA vaccine with only 25% developing a positive spike-IgG response following two doses of vaccine [46]. Optimal approaches to achieving immunity may require mixing of vaccines and giving extra-doses.

Post-Acute Sequelae of COVID-19 (PASC)

By May 2020, reports began emerging of longer-term deficits associated with COVID-19 (post-acute sequelae of SARS-CoV-2 infection or PASC) including cardiopulmonary symptoms causing fatigue/weakness and limited endurance, mental health complications including anxiety, depression and post-traumatic stress disorder (PTSD), and cognitive deficits [47]. The diagnostic criteria have not been defined and it is reasonable to assume that not all long-term components of the syndrome have been “observed” [48]. Recent estimates are that the sequelae (namely at least 1 symptom that did not exist prior to COVID-19) may be experienced in up to 50% of patients who have documented SARS-CoV-2 infection [49]. In an additional large Chinese cohort study, at 6 months post COVID, fatigue or muscle weakness was seen in 63%, sleep difficulties in 26%, and anxiety or depression reported in 23% [6]. Given its more recent recognition, there is a relative paucity of data of PASC. From recent reports, it appears that many of the symptoms experienced during the acute COVID-19 illness persist at the time of post-COVID follow up and that the severity of the acute illness does not necessarily determine the severity of symptoms following recovery [6, 48, 50]. In fact, some people experiencing the most severe symptoms of PASC may have had mild or no symptoms at the time of the acute infection. To date, no reports have been noted in the literature of patients with CF who have experienced PASC. Given the COVID clinical illness in CF tends to be mild, one might hypothesize that we should be hearing reports of patients with PASC. To date, this has not been the case. As PASC becomes better defined and if new biomarkers can be discovered that are associated with the diagnosis, PASC might be better recognized. The CF community should be cognizant that there is a real possibility that up to 30% of our patients may develop this syndrome.

Conclusion

Overall, the SARS-CoV-2 pandemic has had important impacts on the CF community (persons with CF, their care givers and care provider teams). While there does not appear to be an increase risk of SARS-CoV-2 in persons with CF, subsets of patients are at risk for severe sequelae. Given the pandemic is ongoing, much remains unknown regarding the impact of the pandemic on CF. Continued surveillance and vigilance will be required by

persons with CF, their care givers and care teams to try to mitigate the impact with a strong focus on vaccination.

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Reference section

one bullet (*) for special interest and two bullets (**) for outstanding interest.

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Key points:

- The course of COVID-19 is usually mild in CF patients
- Patients with advanced CF lung disease are at higher risk of respiratory failure
- CF patients living with lung transplantation are at higher risk of severe outcome
- All CF patients should be proposed anti-SARS-CoV-2 vaccination
- Long-term impact of the COVID-19 pandemic on the CF population remains to be established