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COVID-19 in Patients with Chronic Lung Disease

Jessica Fae Calver[a], Laura Fabbri, MD[b], James May, MBBS, MRCP[c], R. Gisli Jenkins, MD, PhD, FRCP, FERS[b,*]

KEYWORDS

• Chronic lung disease • Asthma • COPD • Cystic fibrosis • Interstitial lung disease
• Pulmonary arterial hypertension • COVID-19 susceptibility • Vaccination

KEY POINTS

- Severe acute respiratory syndrome coronavirus 2 infection targets the respiratory epithelium.
- Patients with chronic lung disease (CLD) are at risk of more severe coronavirus disease 2019 (COVID-19).
- Patients with CLD should continue with standard therapy, although patients receiving immunosuppression, particularly rituximab, are at higher risk of infection and severe disease.
- Patients with CLD do not seem at higher risk of adverse vaccine reactions and therefore should be offered vaccination, which reduces the chance of severe COVID-19.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that leads to an acute respiratory tract infection, and for the first couple of years of the pandemic, it lead to acute lung injury in a substantial proportion of people. The combination of improved therapy, vaccination, and mutant strains with a lower trophism for alveolar epithelium seem to have reduced the number of people overall with severe respiratory complications of severe coronavirus disease 2019 (COVID-19). However, patients with a preexisting chronic lung disease (CLD) may have an increased risk of acquiring SARS-CoV-2 infection and also have an increased risk of COVID-19 following with poor outcomes.[1–3] It is therefore crucial to understand the interaction between SARS-CoV-2 and the respiratory tract, especially in patients with compromised pulmonary physiology, to understand the pathogenesis of severe COVID-19 and complications such as "long COVID."

MECHANISMS OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 INFECTION IN THE LUNG

Severe COVID-19 has been associated with SARS-CoV-2 infection of the lower respiratory tract with the primary site of infection being type II alveolar epithelial cells (AT2) in the distal lung.[4] Early in February 2020, it was reported that the major mechanism for SARS-CoV-2 viral entry into cells was through angiotensin-converting enzyme 2 (ACE2) expressed on the cell surface.[5] Yet, single-cell RNA-sequencing and protein atlas assessment of ACE2 determined low ACE2 gene expression and rare ACE2 protein expression in the airway epithelium and alveoli of control and CLD groups.[4,6] The low level of ACE2 expression at the major site of infection within the lungs suggests that it is likely that alternative non-ACE2–mediated mechanisms of cell infection exist in the lung and that these might be responsible for the

[a] University of Nottingham, Medical School, Nottingham NG7 2UH, United Kingdom; [b] National Heart and Lung Institute, Imperial College London, Guy Scadding Building, Cale Street, London SW3 6LY, United Kingdom; [c] Guy's and St Thomas' NHS Trust, Westminster Bridge SE1 7EH, United Kingdom
* Corresponding author.
E-mail address: Gisli.jenkins@imperial.ac.uk

Clin Chest Med 44 (2023) 385–393
https://doi.org/10.1016/j.ccm.2022.11.013

worse outcomes of patients with CLD. The virus has been shown to use several coreceptors including CD147/Basigin/BSG; NRP1 (Neuropilin-1); GRP78 (78 kDa glucose-regulated protein)/HSPA5 (Heat Shock Protein Family A (Hsp70) Member 5); and proteases Transmembrane serine protease 2 (TMPRSS2), Cathepsin L/CTSL (cathepsin L), FURIN (Furin), and ADAM17 (A disintegrin and metalloprotease 17) to facilitate infection.[1,4,7–13] Difference in these coreceptors explain the different pathogenicity of the newer Omicron variants[14]; however, the overall differences in SARS-CoV-2 entry factors are minimal in CLD, suggesting that viral entry alone does not explain the variation in disease severity observed between patients with and without CLD.[4] More recently, it has been hypothesized that in addition to increased susceptibility to infection, CLD patients have altered expression profiles of antiviral and immune response genes, altering their alveolar microenvironment and ability to fight infection. Having impaired innate immunity reduces the antiviral defense, which may promote host permissiveness and an increase in viral replication. As a result, they may be predisposed to severe lung injury.[4]

Although CLD has been cited as a risk factor for severe COVID-19, the different types of CLD have distinct pathologic mechanisms and treatment modalities. Subsequently, the molecular characteristics influencing SARS-CoV-2 severity differ between the groups.

ASTHMA

Asthma is an inflammatory condition of the airways occurring in all age groups but is more common in younger patients and is commonly associated with allergic diseases such as rhinosinusitis. Exacerbations of asthma are frequently caused by viral infections including rhinovirus and influenza and may be life-threatening. Asthma patients have impaired type-I interferon (IFN-I) responses, yet the risk of severe COVID-19 differs between the 2 main asthma endotypes: type-2 (allergic and eosinophilic) versus non-type-2 (neutrophilic and paucigranulocytic).[15]

In type-2 asthma, the proinflammatory cytokines interleukin (IL)-4, IL-5, and IL-13 are secreted to drive a Th2-type immune response, which perhaps modulates SARS-CoV-2 infectivity with IL-13 shown to downregulate ACE2 expression by airway epithelial cells (AECs).[16–18] In addition, type-2 cytokines and IgE cross-linking have previously been shown to suppress toll-like receptor (TLR) expression, possibly preventing an IFN-driven upregulation of ACE2.[19,20] Yet IL-13 increases TMPRSS2 expression, although a low frequency of dual ACE2+/TMPRSS2+ expressing cells are present for viral entry.[18] It has been suggested that the preventative inhaled corticosteroid (ICS), ciclesonide, may even have inhibitory effects on viral replication by binding to the SARS-CoV-2 viral endonuclease NSP15.[21,22] In a randomized trial, patients treated with ciclesonide had reduced hospital attendance, although symptom duration was not reduced.[23] Additional protective factors in type-2 asthma patients include eosinophilia contributing to antiviral immunity and preexisting ICS usage for the long-term management of asthma.[24] Preexisting eosinophilia (>150 cells/μL) was protective against hospital admission, and the development of eosinophilia during admission was protective against mortality.[25] Consequently, concerns are raised regarding the use of biologic agents that directly interfere with Th2 inflammation and eosinophil function, yet their use is lifesaving in those with the worst forms of asthma. Reassuringly, a large cohort study did not find higher prevalence or worse outcomes in asthma patients on biologic therapy.[26]

By comparison, it has been suggested that individuals with non-type-2 asthma have an increased risk of severe COVID-19. In non-type-2 asthma, there is a greater involvement of Th1 and Th17 responses, predominantly through the cytokines IL-1β, IL-8, IL-6, and IL-17, many of which play a central role in the "cytokine storm."[15] Non-type-2 cytokines have been associated with an increased expression of ACE2 in epithelial cells, which may increase SARS-CoV-2 infection and similarly these individuals have low eosinophil levels, which usually have a protective role in viral infection.[27] Adding to this, IL-17 induces neutrophil migration during asthma onset, and these neutrophil levels (%) have been shown to significantly associate with FURIN gene expression in sputum.[28]

The different responses of eosinophilic and neutrophilic phenotypes may be the cause of conflicting data from studies of asthmatic patient. Early large-scale studies concluded that there was a higher incidence of COVID-19 in patients with asthma that there was a higher risk of severe COVID-19 (although asthma was not an independent risk factor) and that asthma treatment including biologic therapy did not influence disease course.[29,30] However, a more recent meta-analysis found that the risk of contracting COVID-19 was lower in patients with asthma versus nonasthmatics, and importantly, there were no significant differences in hospitalization, intensive care admission, or mechanical ventilation requirements.[31] Although once intubated, asthma patients are more likely to require longer periods of mechanical ventilation, which has been identified as an independent risk factor.[32]

Few cases of asthma exacerbation after COVID-19 vaccination have been reported.[33] However, the overall benefit of vaccination against SARS-CoV-2 outweighs the extremely low overall risk of an allergic reaction should not discourage the vaccination.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease characterized by airway inflammation and alveolar destruction.[34] Expiratory airflow limitation with an FEV1/FVC ratio of less than 0.7 is diagnostic and the condition is associated with former smoking, current smoking, or noxious fume exposure. Pharmacotherapy includes bronchodilators and in certain cases ICS.[35] Acute exacerbations of COPD are characterized by worsening symptoms relative to the stable state, which frequently cause hospitalization and lung function deterioration in this patient group. An exacerbation is commonly triggered by infection, particularly viruses.[36] Subsequently, the emergence of SARS-CoV-2 raised concerns about the deleterious influence COVID-19 may have on the "clinically extremely vulnerable" patients with COPD with an increased risk of mortality.[37–39] Patients with COPD are at higher risk of hospitalization and have 4-fold higher risk of developing severe COVID-19.[38,40]

Patients with COPD have dampened IFN-I responses, which may consequently increase the risk of SARS-CoV-2 infection in the airway epithelium.[41] Recent evidence has implicated a reduction in the expression of the pattern recognition receptors (PRRs) retinoic acid-inducible gene I-like receptors and melanoma differentiation-associated protein 5.[41] These PRRs are a part of the innate immunity defense and recognize pathogen-associated molecular patterns and/or damage-associated molecular patterns to induce an antiviral IFN-I response. In addition, the expression of the type-I interferon IFN-β and its transcription factor IRF-7 are also decreased in patients with COPD.[41,42] In contrast, TLR2 and TLR4 expressions are increased in patients with COPD, which may be driving inflammation and an IFN-driven upregulation of the interferon-stimulated gene ACE2.[42–44] Alongside the dysregulation of these immune factors, TMPRSS2 protein expression is upregulated in COPD lung homogenates and NRP1 expression slightly upregulated in COPD macrophages.[4,45] Whether ACE2, CD147, and FURIN are upregulated in COPD to facilitate viral entry remains to be determined.[4,6,45–49]

To date, the overall prevalence of COVID-19 does not seem to be increased in patients with COPD. The impact of smoking on COVID-19 outcomes remains a topic of debate, although never smokers are likely to have better outcomes than current or former smokers.[39] There are several factors that may increase the risk of severe disease with poor outcomes in patients with COPD. Impaired lung function including air flow limitation, hyperinflation with poor inspiratory reserve, reduced gas transfer and impaired host defense blunt the ability to compensate for the vast pathologic condition, which affects the lungs in COVID-19 pneumonitis (inflammatory infiltrates, interstitial edema progressing to ARDS, and thromboembolism/in situ thrombosis).[50,51]

Similar to asthma, patients with COPD have continued with their established management therapies and have not adjusted, withdrawn, or escalated treatment during the COVID-19 pandemic. No harm has been reported with inhaled bronchodilator therapy although ICS is a more contentious issue. It has been demonstrated by in vivo and in vitro studies that ICS attenuate ACE2 receptor expression, yet a large cohort of patients with COPD receiving ICS were reported to be at increased risk of death from COVID-19 compared with those on Long Acting Beta Agonist and Long Acting Muscarinic antagonist (LABA/LAMA) therapy.[52,53] However, there was likely significant unmeasured confounding from disease severity, given that most patients on ICS tend to experience frequent exacerbations and/or have more severe airflow obstruction. The consensus is that inhaled treatment should be continued unaltered in stable patients.[54]

Initially, concerns were raised regarding the management of COPD acute exacerbations with oral corticosteroids. Early in the pandemic, there was significant anxiety over their use, especially given previous data from the Middle East respiratory syndrome coronavirus (MERS-CoV) pandemic.[55] This has now been superseded by the findings of the RECOVERY trial, which demonstrated a mortality benefit of dexamethasone for all patients requiring supplemental oxygen therapy; this is now accepted standard of care for severe COVID-19.[56] Surprisingly, there has been a 50% reduction in hospital admission from COPD exacerbations in prepandemic versus pandemic times. This is likely reflective of patients isolating from the general public resulting in reduced viral transmission (not limited to SARS-CoV-2). Although these observations may guide important public health strategy, significant depression and anxiety associated with social isolation is likely to result.[57] Currently, there is neither evidence of an adverse

effect of COVID-19 vaccines in patients with COPD nor evidence of diminished efficacy.

BRONCHIECTASIS

Bronchiectasis is a condition of abnormally dilated airways and impaired mucociliary clearance. There are various causes including genetic (cystic fibrosis [CF] and primary ciliary dyskinesia), post-infectious (bacterial pneumonia, whooping cough, and tuberculosis), autoimmune (rheumatoid arthritis and inflammatory bowel disease), and immune dysfunction. The architectural distortion of the airways causes chronic sputum production and increased susceptibility to pulmonary infection. In comparison with some other forms of CLD, patients with bronchiectasis have a higher risk of contracting COVID-19, more severe disease, and poorer outcomes.[58] This may relate to the structural pulmonary abnormalities and impaired host defense response causing a greater risk of infection and respiratory failure. Corticosteroid treatments (inhaled or oral) are less commonly used in the chronic management of bronchiectasis or exacerbation management compared with asthma and COPD. Similar to patients with COPD and CF, studies demonstrate a significant decrease in the frequency of reported exacerbations during the COVID-19 pandemic.[59]

CYSTIC FIBROSIS

CF is an autosomal recessive disease affecting the lungs, digestive system, sweat glands, and reproductive tract. The primary abnormality is in chloride and sodium transport across secretory epithelia causing thickened viscous secretions in the bronchi, biliary tract, pancreas, intestines, and reproductive system. Although the disease is systemic, progressive lung disease continues to be the major cause of morbidity and mortality for most patients.[60] The thick airway secretions cause chronic airway obstruction, which gets progressively colonized by pathogenic bacteria. Once infection is established, neutrophils are unable to control the bacteria and release elastase, which overwhelms the antiproteases of the lung and contributes to tissue destruction.[61] In addition, large amounts of DNA and cytosol matrix proteins are released by degranulating neutrophils, contributing to the increased viscosity of the airway mucus. Chronic infection and an ineffective inflammatory response seem to be the major stimulus for an exuberant, which subsequently results in bronchiectasis.[62,63]

Although the sputum levels of IL-6 are lower in patients with CF, which may protect against severe COVID-19, CF patients are still categorized as a high-risk group.[64] ACE2 messenger RNA (mRNA) level is elevated in CF AECs when compared with non-CF cells but TMPRSS2 mRNA level is decreased.[65] CF cells also display elevated FURIN activity, which has been shown to increase TGF-β1 production.[66] Cystic fibrosis transmembrane conductance regulator (CFTR) modulators administered for CF treatment are thought to be protective against severe COVID-19.[67]

To date, the literature suggests that CF individuals seem to be contracting SARS-CoV-2 viral infection at a lower rate compared with the general population. Lower rates of SARS-CoV-2 infection in CF individuals are likely explained by the increased awareness of infection, prevention, and control practices including frequent hand hygiene, mask wearing, and continued social distancing. Although the hospitalization rates are higher in CF than in the general population, individuals with CF seem to have better outcomes than initially anticipated, when compared with other respiratory viral infections. There are no specific concerns regarding the safety of mRNA vaccines in patients with CF. A small cohort study showed that CF patients mounted sufficient antibody responses after immunization irrelevant of CFTR genotype, related comorbidities, or treatment type.[68]

INTERSTITIAL LUNG DISEASE

The term interstitial lung disease (ILD) encompasses a group of respiratory diseases affecting the alveolar parenchyma, with inflammation and/or fibrosis affecting the alveolar interstitium. These alterations cause increased morbidity and mortality. ILDs can have a known etiology such as occupational exposure to mold, metals, chemical substances or drugs, and autoimmune diseases. However, a large number of ILDs have no known cause with idiopathic pulmonary fibrosis (IPF) being the most well studied.[69]

ILD patients have an increased frequency of COVID-19 infection compared with the general population; however, COVID-19 susceptibility differs among the ILD subtypes. The incidence of COVID-19 is higher in patients with IPF; however, patients with sarcoidosis and chronic hypersensitivity pneumonitis do not show increased susceptibility to the disease.[70–73] In addition to increased susceptibility, patients with ILD have more severe disease than those without ILD. After COVID-19 infection, they require more oxygen therapy, intensive care admission, and mechanical ventilation.[73]

In IPF, there is an increase in ACE2 protein expression, specifically in the small airways.[4] There

are also significantly lower plasma levels of soluble ACE2 in patients with pulmonary fibrosis, which normally acts as a decoy protein to neutralize SARS-CoV-2 infectivity.[45] This regional increase in ACE2+ cells in the distal lung alongside an upregulation of the epithelial-restricted αvβ6 integrin in AT2 cells, may explain the increased severity in IPF patients despite overall low ACE2 expression levels.[4] The integrin αvβ6 is critical in the pathogenesis of IPF and is upregulated in the fibrotic regions of an IPF lung.[74] The Arg-Gly-Asp (RGD)-binding integrin was suggested as a coreceptor for SARS-CoV-2 infectivity as unlike any other coronavirus, the SARS-CoV-2 spike protein has acquired an RGD motif.[75] The SARS-CoV-2 spike protein S1 subunit can bind to αvβ6, and its overexpression has been shown to augment ACE2-dependent SARS-CoV-2 pseudoviral entry into epithelial cells. The αvβ6 integrin also mediates TGF-β1 activation in human epithelial cells, and this enhanced TGF-β1 signaling can suppress antiviral IFN-I signaling activity by alveolar macrophages.[74,76–78] This may explain the increased severity in patients with IPF despite overall low-ACE2 expression levels. A positive correlation between NRP1 and FURIN expression also exists in IPF AT2 cells, which may facilitate viral entry.[4] The MUC5B promoter rs35705950 T allele is a genetic risk factor for IPF development and has additionally been associated with COVID-19 but seems to be protective against severe disease, perhaps because MUC5B forms part of the innate immune response.[79] The 2 antifibrotic therapies approved for IPF treatment, nintedanib and pirfenidone, may also protect against severe COVID-19 by attenuating profibrotic pathways and IL-6 cytokine levels.[4] Yet short telomere length is a risk factor for both familial and sporadic IPF and has been shown to be associated with increased COVID-19 infection and disease severity.[80]

Studies have suggested that COVID-19 vaccines may be less effective in immunocompromised patients, who are at increased risk of severe COVID-19.[81] Particularly, those with autoimmune diseases and associated ILDs may fail to mount the desired antibody response with mRNA vaccinations.[82] The lower responses correlated with coexistent ongoing treatments, particularly glucocorticoids, mycophenolate mofetil and rituximab.[83] Similarly, patients with IPF did not mount expected antispike antibody responses to 2 doses of SARS-CoV-2 mRNA, irrespective of current antifibrotic treatment.[84] Anecdotally, acute exacerbation of IPF has been reported after vaccine administration in people with ILD-related autoimmune diseases and IPF. These episodes might suggest that the immune response induced by the vaccine may activate a pathobiological cascades leading to the acute exacerbation in susceptible patients. Still, vaccine-associated exacerbation should be considered a rare event occurring in a small minority of vaccinated patients with IPF.[83,85,86] These cases do however raise an important question, which can only be answered by larger, prospective studies comparing the rate of ILD exacerbations between vaccinated and unvaccinated groups.

PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (PAH) is a vasculopathy characterized by remodeling and thickening of the pulmonary arteries with increased vascular resistance and right heart dysfunction. Early in the COVID-19 pandemic, there was a suggestion that patients with PAH may be protected from severe COVID-19.[87] Successively, large cohort studies showed that cumulative incidence was similar to the general population; however, outcomes were worse with half of patients requiring hospitalization and a 12% rate of mortality.[88]

A possible pathogenic mechanism explaining these findings is the reduction of ACE2 in patients with PAH.[89] This downregulation leads to higher circulating levels of angiotensin II with worsened ensuing lung.[90] PAH-specific therapies, including the endothelin receptor antagonists and phosphodiesterase type 5 inhibitors, are also very likely to be important. Endothelin I stabilizes ACE2 expression, which may not only enhance viral binding and replication but also protect against high expression of angiotensin II. Similarly, some of these agents may have anti-inflammatory and antithrombotic properties. However, most importantly their vasodilatory effect may worsen V:Q mismatch by enhancing blood flow to poor ventilated areas of lung and worsening hypoxemia.[91]

It is recommended that established PAH therapy is continued unchanged in the face of infection with COVID-19. However, this patient group may display a more challenging management approach regarding oxygen and ventilatory support. Positive-pressure ventilation (including high flow nasal oxygen, continuous positive airway pressure, and bilevel positive airway pressure) is often used to manage severe hypoxemia, as a bridge or to delay intubation. However, increased airway pressure from these modalities may decrease venous return to the right ventricle and worsen the already struggling cardiopulmonary hemodynamic, making these patients unstable. Similarly, invasive ventilation requires general anesthesia to manage an anticipated reduction in vascular tone and worsening right heart failure. In

these situations, patients may require vasopressor support, which presents its own challenges.[92] No evidence of contraindication of COVID-19 vaccines in patients with pulmonary hypertension has been reported nor is there evidence of diminished vaccine efficacy in this group of patients.

SUMMARY

In summary, the presence of some preexisting CLD may increase the risk of contracting COVID-19, which frequently leads to worse outcomes including increased disease severity and mortality. However, the baseline health status and comorbidities also influence the evolution of COVID-19, and these need to be evaluated in the context of CLD. No evidence currently supports the change of chronic therapy, nor is there convincing evidence of an increased risk of adverse reaction to COVID-19 vaccination thus vaccine uptake should be encouraged. There continues to be a considerable health burden of COVID-19 in patients with CLD, and health-care policy should prioritize the use of antiviral therapies in these vulnerable patients.

CLINICS CARE POINTS

- Patients with Chronic Lung Disease are at increased risk of severe COVID-19 and its complications.
- Patients with Chronic Lung Disease should be prioritised for anti-viral therapy.
- Patients with Chronic Lung Disease are not at increased risk of adverse reactions to COVID-19 vaccines and should be encouraged to have vaccination.

DISCLOSURE

RGJ: Astra Zeneca; Biogen; Galecto; GlaxoSmithKline; Nordic Biosciences RedX; Pliant; Bristol Myers Squibb; Chiesi; Cohbar; Daewoong; Veracyte; Resolution Therapeutics; Boehringer Ingelheim; Chiesi; Roche; PatientMPower; Galapagos; Vicore; NuMedii; Action for Pulmonary Fibrosis.

ACKNOWLEDGEMENTS

UKRI Covid-19 Rapid Response - (EP/V051490/1) The UK Interstitial Lung Disease Long-COVID19 study (UKILD-Long COVID): understanding the burden of Interstitial Lung Disease in Long COVID.

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