SARS-CoV-2 pandemic: clinical picture of COVID-19 and implications for research

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic represents an extraordinary medical challenge that has already had massive economic and societal impacts. In contrast to the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus outbreaks, every respiratory physician and intensivist are likely to encounter patients infected with SARS-CoV-2 and need a good understanding of the management of the associated disease, COVID-19. We are facing the first wave of the SARS-CoV-2 pandemic, but the infectivity of the virus and the lack of population immunity suggest future waves are possible. For this article (summarised in table 1), we have used our recent clinical experience of COVID-19 combined with the limited published data to discuss how the clinical presentation relates to pathogenesis, key research questions and particular issues relevant to respiratory medicine.

Most infections with SARS-CoV-2 are mild, but a minority of patients develop COVID-19 pneumonia. The main differential diagnosis for COVID-19 is community-acquired pneumonia (CAP), which is also commonly caused by infection with respiratory viruses. However, COVID-19 has several clinical features distinct to CAP, which both indicate the diagnosis and suggest it has distinct mechanisms of pathogenesis. For patients with CAP, symptoms, signs and alveolar consolidation usually develop rapidly after infection, whereas for patients with COVID-19, a 6+-day lag between the start of infective symptoms and admission with pneumonia is usual.[1 2] COVID-19 also often causes marked malaise and extrapulmonary symptoms, such as anosmia, headache, myalgia and myocarditis.[3 4] The leading cause of death in COVID-19 is respiratory failure from extensive lung injury. This usually presents with severe hypoxaemia yet highly compliant lungs, and only later develops physiological features usually found in acute respiratory distress syndrome (ARDS), such as high airway pressures and hypercapnia. COVID-19 pneumonia is strikingly slow to improve, and patients require oxygen support for days with a mean duration of hospital admission of 16 days.[1] The radiology of COVID-19 pneumonia is also distinct from CAP, causing basal atelectasis and bilateral poorly defined infiltrates on chest radiographs rather than lobar consolidation.[3] The CT scan abnormalities in COVID-19 are uncommon in other causes of pneumonia, with focal areas of ground-glass infiltrates, peripheral patchy consolidation similar to an organising pneumonia or ARDS-like widespread extensive bilateral infiltrates.[5 6]

In keeping with the clinical picture SARS-CoV-2, viral RNA is detected in sputum later than in nasal samples,[7] but the mechanisms driving COVID-19 pneumonia and how it is sustained over days are uncertain. Without a better understanding of the pathogenesis, why COVID-19 pneumonia only affects a minority of SARS-CoV-2-infected subjects and what constitutes optimum management will remain speculative. An unanswered question is whether severity is proportional to viral load. Severe COVID-19 cases routinely present with lymphopenia and (in contrast to other viral pneumonias) biochemical evidence of severe systemic inflammation, including raised C reactive protein, fibrinogen, D-dimers, lactate dehydrogenase, troponin and ferritin levels.[1–3] These features (partly shared with haemophagocytic lymphohistiocytosis), the delay in development of severe disease and the radiology suggest that the lung infiltrates may be caused by an excessive inflammatory response to SARS-CoV-2. Abnormalities consistent with thrombotic microangiopathy are also common in severe disease, suggesting some of the pathology is driven by endothelial activation and thrombosis. Two potential overlapping stages of COVID-19 are plausible: an initial 'standard' viral infection followed by a hyperinflammatory response in the subset of severely affected patients. Clinical trials have started assessing the efficacy of the early use of antivirals, and many immunomodulatory approaches, including, but not restricted to, corticosteroids, macrolides, hydroxychloroquine, blockade of interleukin (IL)-6 (eg, tocilizumab and sarilumab), IL-1 (eg, anakinra) or granulocyte-macrophage colony-stimulating factor (GM-CSF), plasma exchange and hyperimmune serum. The risk–benefit of these agents requires careful consideration, and the rapid identification of COVID-19 endotypes that benefit from specific treatment modalities is challenging. Defining clinically relevant and treatment-responsive patient subpopulations will be critical for effective management and will require integration of clinical, imaging, virology, immunological and inflammatory biomarker data at key timepoints during disease development and in response to different therapies.

The mortality of COVID-19 increases in patients with hypertension, diabetes or obesity, and markedly so with age.[8] Important questions are whether this is causal or an epiphenomenon, and why these subgroups are targeted. Could this be a manifestation of pre-existing microvascular disease, 'inflammaging' (chronic low-grade inflammation in the elderly) or immunosenescence (age-related impairment of innate and adaptive immunity)? The pathogenetic mechanisms underlying severe COVID-19 may vary between the elderly and younger adults, potentially requiring a different management strategy. Other unexplained features of severe COVID-19 are the male preponderance, with 65%–70% of deaths occurring in men,[1 3] and the higher incidence in black, Asian and minority ethnic (BAME) background subjects. The male preponderance may relate in part to the effects of sex on disease pathogenesis, whereas the high incidence of disease in BAME subjects could reflect biological effects of ethnicity, the incidence of comorbidities and/or socioeconomic factors.

The most important clinical manifestation of COVID-19 is hypoxaemia, successful management of which is essential for a good outcome. The severity of hypoxaemia can be out of proportion to a patient's apparent dyspnoea, so accurate and continuous monitoring of oxygenation is essential. A high proportion of patients with COVID-19 pneumonia need prolonged ventilatory support (>10–14 days). CPAP could be a practical option as

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Table 1 Summary of COVID-19 disease features, the research questions these raise, and potential therapeutic relevance

Disease features	Research question	Potential therapeutic consequences
Clinical/demographic		
Delay between infection and pneumonia	Related to later viral replication in the lung? Abnormal inflammation in a subset of infected subjects? Related to development of adaptive immunity?	Antiviral treatment to prevent severe disease Immunomodulation to prevent severe disease
Variable severity within an age group	Driven by viral load? Driven by genetics/epigenetics? Driven by environmental factors?	Improved identification of at-risk subjects Targeted antiviral/immunodulation treatments to prevent severe disease in at-risk subjects
Increased severity with age/male sex/comorbidities	Related to comorbidities alone? Direct effects on the inflammatory response? Related to 'inflammaging'/immunosenescence?	Improved identification of at-risk subjects Targeted antiviral/immunodulation treatments to prevent severe disease in at-risk subjects
High burden of disease in BAME background	Related to ACE2 expression, comorbidities and/or socioeconomic factors?	Improved identification of at-risk subjects
Prolonged disease course	What mechanisms maintain the lung infiltrations?	Therapies to help clear pneumonic infiltrates
High mortality	Detailed postmortem studies to identify causes	Improved management of severe cases
Investigations/radiology/physiology		
Marked increase in inflammatory markers	What are the mechanisms driving inflammation? What cells are the source of inflammatory responses? Does inflammation cause poor outcomes?	Clinical risk scoring Improved anti-inflammatory treatment
Variations between patients in inflammatory markers	Relationship to disease subtypes and outcome?	Endotyping for targeted treatments
Evidence of cardiac/other extrapulmonary disease	Role for poor outcomes?	Specific targeted therapies
Evidence for microangiopathic and macroangiopathic thromboses	Role for disease pathogenesis/poor outcomes?	Potential role for anticoagulation
Radiological patterns	Relationship to clinical severity? Relationship between the CT patterns over time? Relationship between CT patterns and pathogenesis?	Clinical risk scoring Endotyping for targeted treatments
Severe hypoxia with low compliance ventilation	What are the pathophysiological mechanisms? What is the role of CPAP? What is the best ventilation strategy?	Improved ventilatory support strategies Pharmacological enhancement of oxygenation
Specific issues for respiratory physicians		
Survivors of severe COVID-19 pneumonia	Is there a long-term reduction in lung function? If so, who is at risk and is this related to management? Are there other physical/psychological consequences?	Screening for impaired lung function Acute management to reduce lung function loss Appropriate postdischarge support
Patients with chronic lung disease	Which patients with chronic lung disease are susceptible? What mechanisms cause the increased susceptibility? Can antivirals prevent severe COVID-19? What proportion of patients are immune?	Improved identification of at-risk subjects Early use of preventative therapies Early use of antivirals Targeted vaccination in high-risk subjects

BAME, black, Asian and minority ethnic; CPAP, continuous positive airways pressure.

an alternative to mechanical ventilation in a subset of patients, given that high patient load can overwhelm ventilator provision.

The SARS-CoV-2 pandemic has major implications for patients with chronic respiratory disease. COVID-19 infection in patients with COPD is 2.7 times more likely to have an adverse outcome,[4] though it is not clear whether this relates to poor lung reserve or if COPD impairs viral clearance and/or negatively impacts the inflammatory response to SARS-CoV-2. In addition, whether other chronic lung diseases, their treatment or smoking history alone increases the risk of severe COVID-19 is uncertain. The prevalence and efficacy of postinfective immunity to SARS-CoV-2 need to be determined in patients with chronic lung disease to help target future vaccination programmes. Data are needed on the long-term effects of severe COVID-19; the high prevalence of extensive lung injury suggests there could be permanent loss of lung function, as well as other physical, cognitive and behavioural issues.

The challenge of COVID-19 is requiring a massive clinical effort, and there is a parallel concerted academic approach to address key research priorities. The efficacy of lopinavir–ritonavir (antivirals used to treat HIV), low-dose dexamethasone, hydroxychloroquine and inhaled interferon is being evaluated in the world's largest COVID-19 clinical trial, Randomised Evaluation of COVID-19 Therapy trial, (endorsed by the UK Chief Medical Officer). COVID-19 has been integrated into the global Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia platform with treatment arms, including lopinavir/ritonavir, hydroxychloroquine, macrolides, corticosteroids, interferon beta-1a and the IL-1 receptor antagonist anakinra. Other immunomodulatory therapies being investigated include monoclonal antibodies targeting the IL-6 receptor antibodies, for example, tocilizumab (NCT04320615) and sarilumab (NCT04327388); IL-6, for example, siltuximab (NCT04329650); or the GM-CSF receptor, for example, lenzilumab (NCT04351152). Trials of the experimental antiviral remdesivir or of convalescent serum therapy (eg, NCT04345523) are either ongoing or about to start recruiting. Despite the warnings provided by SARS and MERS, our understanding of the pathogenesis of coronavirus pneumonia remains poor. Hence, alongside multicentre clinical trials, there is a need for translational and basic science

research which will require expansion of category 3 laboratory facilities capable of handling SARS-CoV-2-infected samples. These academic efforts will be essential to improve our understanding of both the pathogen and the host response so we can reduce the future morbidity and mortality caused by COVID-19 or other potential novel viral pneumonias.

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