SARS-CoV2 pandemic: the clinical picture of COVID-19 and implications for research

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The SARS-CoV2 pandemic represents an extraordinary medical challenge that has already had massive economic and societal impacts. In contrast to the SARS and MERS coronavirus outbreaks, every respiratory physician and intensivist is likely to encounter patients infected with SARS-CoV2 and need a good understanding of the management of the associated disease COVID-19. We are facing the first wave of the SARS-CoV2 pandemic, but the infectivity of the virus and 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 for respiratory medicine.

Most infections with SARS-CoV2 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. With CAP, symptoms, signs and alveolar consolidation usually develop rapidly after infection, whereas for COVID-19 patients a 6+ day lag between the start of infective symptoms and admission with pneumonia is usual1,2. COVID-19 also often causes marked malaise and extrapulmonary symptoms such as anosmia, headache, myalgia, and myocarditis3,4. 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 days1. 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 consolidation3. 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 (OP), or ARDS-like widespread extensive bilateral infiltrates5,6.
In keeping with the clinical picture SARS-CoV2 viral RNA is detected in sputum later than in nasal samples, 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-CoV2 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. 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-CoV2. 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 (e.g. tocilizumab, sarilumab), IL-1 (e.g. anakinra) or 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. 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 is the male preponderance, with 65-70% of deaths occurring in men\textsuperscript{1,3}, and the higher incidence in black, Asian and minority ethnic background (BAME) 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 potentially higher expression of ACE2 (the SARS-CoV-2 receptor), 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 COVID-19 pneumonia patients need prolonged ventilatory support (>10-14 days). CPAP could be a practical option as an alternative to mechanical ventilation in a subset of patients given that high patient load can overwhelm ventilator provision.

The SARS-CoV2 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\textsuperscript{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-CoV2. In addition, whether other chronic lung diseases, their treatment, or smoking history alone increase the risk of severe COVID-19 is uncertain. The prevalence and efficacy of post-infective immunity to SARS-CoV2 needs to be determined in chronic lung disease patients 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 suggest 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 are being evaluated in the world's largest COVID-19 clinical trial, RECOVERY (Randomised Evaluation of COVID-19 Therapy)
trial, endorsed by the UK Chief Medical Officer). COVID19 has been integrated into
the global REMAP-CAP platform (Randomised, Embedded, Multi-factorial, Adaptive
Platform Trial for Community-Acquired Pneumonia) 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 interleukin-6 (IL-6) receptor
antibodies e.g. tocilizumab (NCT04320615) and sarilumab (NCT04327388), IL-6 e.g.
siltuximab (NCT04329650), or the GM-CSF receptor e.g. lenzilumab (NCT04351152).
Trials of the experimental anti-viral remdesivir or of convalescent serum therapy (e.g.
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 multi-centre 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-CoV2 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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