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 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 (OP), or ARDS-like widespread extensive bilateral infiltrates[5,6].

58   In keeping with the clinical picture SARS-CoV2 viral RNA is detected in sputum later

59   than in nasal samples[7], but the mechanisms driving COVID-19 pneumonia and how it

60   is sustained over days are uncertain. Without a better understanding of the

61   pathogenesis, why COVID-19 pneumonia only affects a minority of SARS-CoV2

62   infected subjects, and what constitutes optimum management will remain speculative.

63   An unanswered question is whether severity is proportional to viral load. Severe

64   COVID-19 cases routinely present with lymphopenia and (in contrast to other viral

65   pneumonias) biochemical evidence of severe systemic inflammation, including raised

66   C-reactive protein, fibrinogen, D-dimers, lactate dehydrogenase, troponin and ferritin

67   levels[1,2,3]. These features (partly shared with haemophagocytic lymphohistiocytosis),

68   the delay in development of severe disease, and the radiology suggest that the lung

69   infiltrates may be caused by an excessive inflammatory response to SARS-CoV2.

70   Abnormalities consistent with thrombotic microangiopathy are also common in severe

71   disease, suggesting some of the pathology is driven by endothelial activation and

72   thrombosis. Two potential overlapping stages of COVID-19 are plausible: an initial

73   'standard' viral infection followed by a hyperinflammatory response in the subset of

74   severely affected patients. Clinical trials have started assessing the efficacy of the

75   early use of antivirals, and many immunomodulatory approaches including, but not

76   restricted to corticosteroids, macrolides, hydroxychloroquine, blockade of interleukin

77   (IL)-6 (e.g. tocilizumab, sarilumab), IL-1 (e.g. anakinra) or GM-CSF, plasma exchange,

78   and hyperimmune serum. The risk / benefit of these agents requires careful

79   consideration, and the rapid identification of COVID-19 endotypes that benefit from

80   specific treatment modalities is challenging. Defining clinically relevant and treatment-

81   responsive patient subpopulations will be critical for effective management, and will

82   require integration of clinical, imaging, virology, immunological, and inflammatory

83   biomarker data at key timepoints during disease development and in response to

84   different therapies.

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86   The mortality of COVID-19 increases in patients with hypertension, diabetes or

87   obesity, and markedly so with age[8]. Important questions are whether this is causal or

88   an epiphenomenon, and why these subgroups are targeted? Could this be a

89   manifestation of pre-existing microvascular disease, 'inflammaging' (chronic low-

90   grade inflammation in the elderly) or immunosenescence, (age-related impairment of

91   innate and adaptive immunity)? The pathogenetic mechanisms underlying severe

92   COVID-19 may vary between the elderly and younger adults, potentially requiring a
93   different management strategy. Other unexplained features of severe COVID-19 is the
94   male preponderance, with 65-70% of deaths occurring in men[1,3], and the higher
95   incidence in black, Asian and minority ethnic background (BAME) subjects. The male
96   preponderance may relate in part to the effects of sex on disease pathogenesis,
97   whereas the high incidence of disease in BAME subjects could reflect potentially
98   higher expression of ACE2 (the SARS-CoV-2 receptor), the incidence of comorbidities
99   and / or socioeconomic factors.

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101   The most important clinical manifestation of COVID-19 is hypoxaemia, successful
102   management of which is essential for a good outcome. The severity of hypoxaemia
103   can be out of proportion to a patient's apparent dyspnoea, so accurate and continuous
104   monitoring of oxygenation is essential. A high proportion of COVID-19 pneumonia
105   patients need prolonged ventilatory support (>10-14 days). CPAP could be a practical
106   option as an alternative to mechanical ventilation in a subset of patients given that
107   high patient load can overwhelm ventilator provision.

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109   The SARS-CoV2 pandemic has major implications for patients with chronic respiratory
110   disease. COVID-19 infection in patients with COPD is 2.7 times more likely to have
111   an adverse outcome[4], though it is not clear whether this relates to poor lung reserve
112   or if COPD impairs viral clearance and/or negatively impacts the inflammatory
113   response to SARS-CoV2. In addition, whether other chronic lung diseases, their
114   treatment, or smoking history alone increase the risk of severe COVID-19 is uncertain.
115   The prevalence and efficacy of post-infective immunity to SARS-CoV2 needs to be
116   determined in chronic lung disease patients to help target future vaccination
117   programmes. Data are needed on the long-term effects of severe COVID-19; the high
118   prevalence of extensive lung injury suggest there could be permanent loss of lung
119   function as well as other physical, cognitive and behavioural issues.

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121   The challenge of COVID-19 is requiring a massive clinical effort, and there is a parallel
122   concerted academic approach to address key research priorities. The efficacy of
123   lopinavir-ritonavir (antivirals used to treat HIV), low-dose dexamethasone,
124   hydroxychloroquine and inhaled interferon are being evaluated in the world's largest
125   COVID-19 clinical trial, RECOVERY (Randomised Evaluation of COVID-19 Therapy

126 trial, endorsed by the UK Chief Medical Officer). COVID19 has been integrated into
127 the global REMAP-CAP platform (Randomised, Embedded, Multi-factorial, Adaptive
128 Platform Trial for Community-Acquired Pneumonia) with treatment arms including
129 lopinavir/ritonavir, hydroxychloroquine, macrolides, corticosteroids, interferon beta-1a,
130 and the IL-1 receptor antagonist anakinra. Other immunomodulatory therapies being
131 investigated include monoclonal antibodies targeting the interleukin-6 (IL-6) receptor
132 antibodies e.g. tocilizumab (NCT04320615) and sarilumab (NCT04327388), IL-6 e.g.
133 siltuximab (NCT04329650), or the GM-CSF receptor e.g. lenzilumab (NCT04351152).
134 Trials of the experimental anti-viral remdesivir or of convalescent serum therapy (e.g.
135 NCT04345523) are either ongoing or about to start recruiting. Despite the warnings
136 provided by SARS and MERS, our understanding of the pathogenesis of coronavirus
137 pneumonia remains poor. Hence, alongside multi-centre clinical trials there is a need
138 for translational and basic science research which will require expansion of category
139 3 laboratory facilities capable of handling SARS-CoV2 infected samples. These
140 academic efforts will be essential to improve our understanding of both the pathogen
141 and the host response so we can reduce the future morbidity and mortality caused by
142 COVID-19 or other potential novel viral pneumonias.
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References:

1. Chen T, Wu D, Chen H, *et al.* Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020;368:m1091 doi: 10.1136/bmj.m1091.

2. Zhou F, Ting Y, Ronghui D, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–62

3. Mo P, Xing Y, Xiao Yu, *et al*. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis 2020: pii: ciaa270. doi: 10.1093/cid/ciaa270.

4. Guan W-j, Wen-hua L, Zhao Y, *et al*. Comorbidity and its impact on 1,590 patients with Covid-19 in China: A Nationwide Analysis. *Europ Resp J* 2020: Mar 26. pii: 2000547. doi: 10.1183/13993003.00547-2020.

5. Chen Z, Fan H, Cai J, *et al*. High-resolution computed tomography manifestations of COVID-19 infections in patients of different ages. *European Journal of Radiology* 2020; 126.   doi: https://doi.org/10.1016/j.ejrad.2020.108972

6. Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020 ;395(10223):497-506.   doi: 10.1016/S0140-6736(20)30183-5

7. Wölfel R, Corman VM, Guggemos W, *et al.* Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020 doi: 10.1038/s41586-020-2196-x. PMID:32235945

8. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020: S2213-2600(20)30079-5. doi: 10.1016/S2213-2600(20)30079-5.

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?	Antiviral treatment to prevent severe disease
	Abnormal inflammation in a subset of infected subjects?	Immunomodulation to prevent severe disease
	Related to development of adaptive immunity?	
Variable severity within an age group	Driven by viral load?	Improved identification of at risk subjects
	Driven by genetics / epigenetics?	Targeted antiviral / immunodulation treatments to
	Driven by environmental factors?	prevent severe disease in at risk subjects
Increased severity with age / male sex / comorbidities	Related to comorbidities alone?	Improved identification of at risk subjects
	Direct effects on the inflammatory response?	Targeted antiviral / immunodulation treatments to
	Related to 'inflammaging' / immunosenescence?	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 post-mortem studies to identify cause(s)	Improved management of severe cases
Investigations / radiology / physiology		
Marked increase in inflammatory markers	What are the mechanisms driving inflammation?	Clinical risk scoring
	What cells are the source of inflammatory responses?	Improved anti-inflammatory treatment
	Does inflammation cause poor outcomes?	
Variations between patients in inflammatory markers	Relationship to diseases subtypes and outcome?	Endotyping for targeted treatments
Evidence for cardiac / other extra-pulmonary disease	Role for poor outcomes?	Specific targeted therapies
Evidence for micro- and macroangiopathic thrombosis	Role for disease pathogenesis / poor outcomes?	Potential role for anticoagulation
Radiological patterns	Relationship to clinical severity?	Clinical risk scoring
	Relationship between the CT patterns over time?	Endotyping for targeted treatments
	Relationship between CT patterns and pathogenesis?	
Severe hypoxia with low compliance ventilation	What are the pathophysiological mechanisms?	Improved ventilatory support strategies
	What is the role of CPAP?	Pharmacological enhancement of oxygenation
	What is the best ventilation strategy?	
Specific issues for respiratory physicians		
Severe COVID-19 pneumonia survivors	Is there a long term reduction in lung function, if so who is at risk and is this related to management?	Screening for impaired lung function
		Acute management to reduce lung function loss
	Are there other physical / psychological consequences	Appropriate post-discharge support
Chronic lung disease patients	Which chronic lung disease patients are susceptible?	Improved identification of at risk subjects
	What mechanisms cause the increased susceptibility?	Early use of preventative therapies
	Can antivirals prevent severe COVID-19?	Early use of antivirals
	What proportion of patients are immune?	Targeted vaccination in high risk subjects