Severe COVID-19 *versus* multisystem inflammatory syndrome: comparing two critical outcomes of SARS-CoV-2 infection

Rupsha Fraser[1], Aurelio Orta-Resendiz[2], David Dockrell[1], Michaela Müller-Trutwin[2] and Alexander Mazein[3]

[1]The University of Edinburgh, Queen's Medical Research Institute, Edinburgh, UK. [2]Institut Pasteur, Université Paris Cité, HIV, Inflammation and Persistence Unit, Paris, France. [3]Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Belvaux, Luxembourg.

Corresponding author: Rupsha Fraser (rupsha.fraser@ed.ac.uk)

Shareable abstract (@ERSpublications)
Development of severe COVID-19 *versus* multisystem inflammatory syndrome relies on distinct aetiological factors that lead to variable host immune responses and inflammatory manifestations, despite following a common trajectory of immune dysregulation. https://bit.ly/3Xtsa7P

Cite this article as: Fraser R, Orta-Resendiz A, Dockrell D, *et al*. Severe COVID-19 *versus* multisystem inflammatory syndrome: comparing two critical outcomes of SARS-CoV-2 infection. *Eur Respir Rev* 2023; 32: 220197 [DOI: 10.1183/16000617.0197-2022].

Received: 14 Oct 2022
Accepted: 31 Dec 2022

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with diverse host response immunodynamics and variable inflammatory manifestations. Several immune-modulating risk factors can contribute to a more severe coronavirus disease 2019 (COVID-19) course with increased morbidity and mortality. The comparatively rare post-infectious multisystem inflammatory syndrome (MIS) can develop in formerly healthy individuals, with accelerated progression to life-threatening illness. A common trajectory of immune dysregulation forms a continuum of the COVID-19 spectrum and MIS; however, severity of COVID-19 or the development of MIS is dependent on distinct aetiological factors that produce variable host inflammatory responses to infection with different spatiotemporal manifestations, a comprehensive understanding of which is necessary to set better targeted therapeutic and preventative strategies for both.

Introduction

The management of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, causing the coronavirus disease 2019 (COVID-19) pandemic, has been a major new challenge to healthcare and research. SARS-CoV-2 infection is associated with diverse host response immunodynamics with variable inflammatory manifestations. The development of severe COVID-19 can typically be linked to a number of risk factors (*e.g.* age-related susceptibility, pre-existing chronic diseases or an immunosuppressed status, amongst others) that cause altered immune profiles [1–7], while another potentially fatal syndrome can develop in previously healthy individuals following SARS-CoV-2 infection, termed multisystem inflammatory syndrome (MIS) [8–10]. Despite a significant overlap in their dysregulated immune responses, these two hyperinflammatory disease phenotypes can be distinguished by a range of distinct spatiotemporal adaptations and clinical profiles. Understanding how different aetiological factors underpin the immunopathogenic pathways and timeline of events in the development of severe COVID-19 and MIS will guide patient stratification and more targeted therapeutic or vaccination strategies. Here, we pinpoint severe COVID-19 as an early acute hyperinflammatory response predominantly affecting the respiratory tract, but also with systemic involvement that is influenced by various risk factors to cause impairment of the primary innate response to infection, as well as dysregulation of downstream innate and adaptive defence mechanisms, and MIS as a delayed acute hyperinflammatory response to SARS-CoV-2 infection with systemic but minimal or no respiratory symptoms and low pulmonary viral loads, which might develop due to genetic susceptibility traits that trigger the activation of systemic autoimmune and hyperinflammatory pathways upon SARS-CoV-2 infection.

SARS-CoV-2 viral entry and primary host response to infection

SARS-CoV-2 binds the peptidase angiotensin converting enzyme 2 (ACE2) *via* its spike (S) glycoprotein [11–13] and SARS-CoV-2 enters cells through direct fusion of the virion and cell membranes *via* cleavage of S by the proteases transmembrane protease serine 2 (TMPRSS2) and furin [13–16] or *via* endocytosis of the SARS-CoV-2 virion in the absence of these proteases [13]. Expression of ACE2, TMPRSS2 and furin (and additional factors that may further support SARS-CoV-2 infectivity and tropism) varies widely according to tissue type, age and biological sex, with different disease conditions, pregnancy or with genetic differences, influencing host susceptibility to infection and viral replication [1, 7, 9, 17–22].

SARS-CoV-2 is a cytopathic virus that causes death and injury of infected cells. Local inflammatory responses extend to lymph nodes and are facilitated by local dendritic cells (DCs) that subsequently travel to draining lymph nodes for antigen presentation to T-cells there and possibly induce immune responses in the spleen [23–25]. Detection of viral RNA by DCs and local macrophages leads to their initiation of a prompt canonical antiviral type 1 interferon (IFN-1) response [26, 27]. IFN-1 signalling concludes with the induction of IFN-stimulated gene (ISG) transcription programmes that interfere with viral replication and activate host immune responses for resolution of infection [28, 29]. Human IFN-1s (including 13 IFN-α subtypes and a single IFN-β subtype) are typically produced at mucosal surfaces by local tissue-resident antigen-presenting cells, with downstream activation of innate and adaptive antipathogenic mechanisms. However, a late, noncanonical hyperinflammatory IFN-1 response can have deleterious immunomodulatory effects that promote viral replication and cause severe complications [28, 30–33]. The timing of IFN-1 signalling relative to peak virus replication is therefore a critical determinant of protective or pathogenic host immune responses [30, 34].

Clinical characteristics of the COVID-19 spectrum and MIS

The COVID-19 spectrum spans from mild–moderate disease to a severe or critical status. The disease course may be classified by four progressive and overlapping phases [35–37], although this classification remains to reach a fully stipulated consensus. First, there appears to be a post-exposure viral phase that may be asymptomatic or mild. During the second phase, detectable upper respiratory viral load decreases as the infection progresses from the upper to the lower respiratory tract, inducing viral pneumonia, which is accompanied by the generation of antibody responses. There is SARS-CoV-2 replication in the upper airways early in the disease course, followed by active replication in the lungs for up to 2 weeks [38]. However, recent data suggests that viral replication in the lower respiratory tract occurs at low levels due to scarce alveolar ACE2 expression and primarily results from a small number of alveolar epithelial type-2 (AT2) cells [39]. Most patients with efficient antiviral defence responses achieve viral clearance and recovery. In patients that develop severe/critical disease, incompetent immune response mechanisms during the second phase are coupled with elevated pro-inflammatory cytokine and acute phase marker release, but the extent to which the dysregulated inflammatory response directly correlates to an incompetent antiviral response is unclear [39, 40]. A third phase corresponds to a state of hypercoagulability in severely affected patients and a fourth phase of multiorgan involvement, damage and failure may follow [35].

A mild–moderate disease course consists of an upper respiratory tract infection with or without symptoms of fever, cough, malaise and possible rare gastrointestinal symptoms [41]. Severe COVID-19 is associated with pneumonia, pulmonary inflammation and injury with significant hypoxia, which leads to some features of acute respiratory distress syndrome (ARDS), hyperinflammation-mediated disruption of the epithelial–endothelial barrier leading to hypercoagulation, vasculopathy, multiorgan damage and circulatory and multiorgan failure [42–44]. Other hyperinflammatory manifestations can include myocardial injury, acute rheumatic manifestations, rhabdomyolysis, septic shock, acute hyperglycaemia, acute renal and hepatic injury, encephalopathy, stroke, and death [23, 41, 45] (figure 1). Excessively high levels of circulating pro-inflammatory cytokines, increased expression of acute phase markers, extensive lymphopenia (with decreasing lymphocyte counts corresponding to disease progression and severity), neutrophilia, coagulopathy and vasculopathy are used as markers of severe disease [26, 44, 46]. SARS-CoV-2 viral persistence is associated with poor outcomes [47].

MIS (originally described in children and adolescents <21 years as MIS-C and subsequently in adults >21 years as MIS-A) is a febrile multisystem hyperinflammatory syndrome that displays features of Kawasaki disease (an acquired paediatric vascular disease), toxic shock syndrome, cardiac dysfunction, acute gastrointestinal conditions and encephalopathy. It is associated with elevated pro-inflammatory cytokines, lymphopenia, neutrophilia, abnormal coagulation indices and multiorgan involvement. While MIS emulates several clinical characteristics of severe COVID-19, it evades severe respiratory illness but

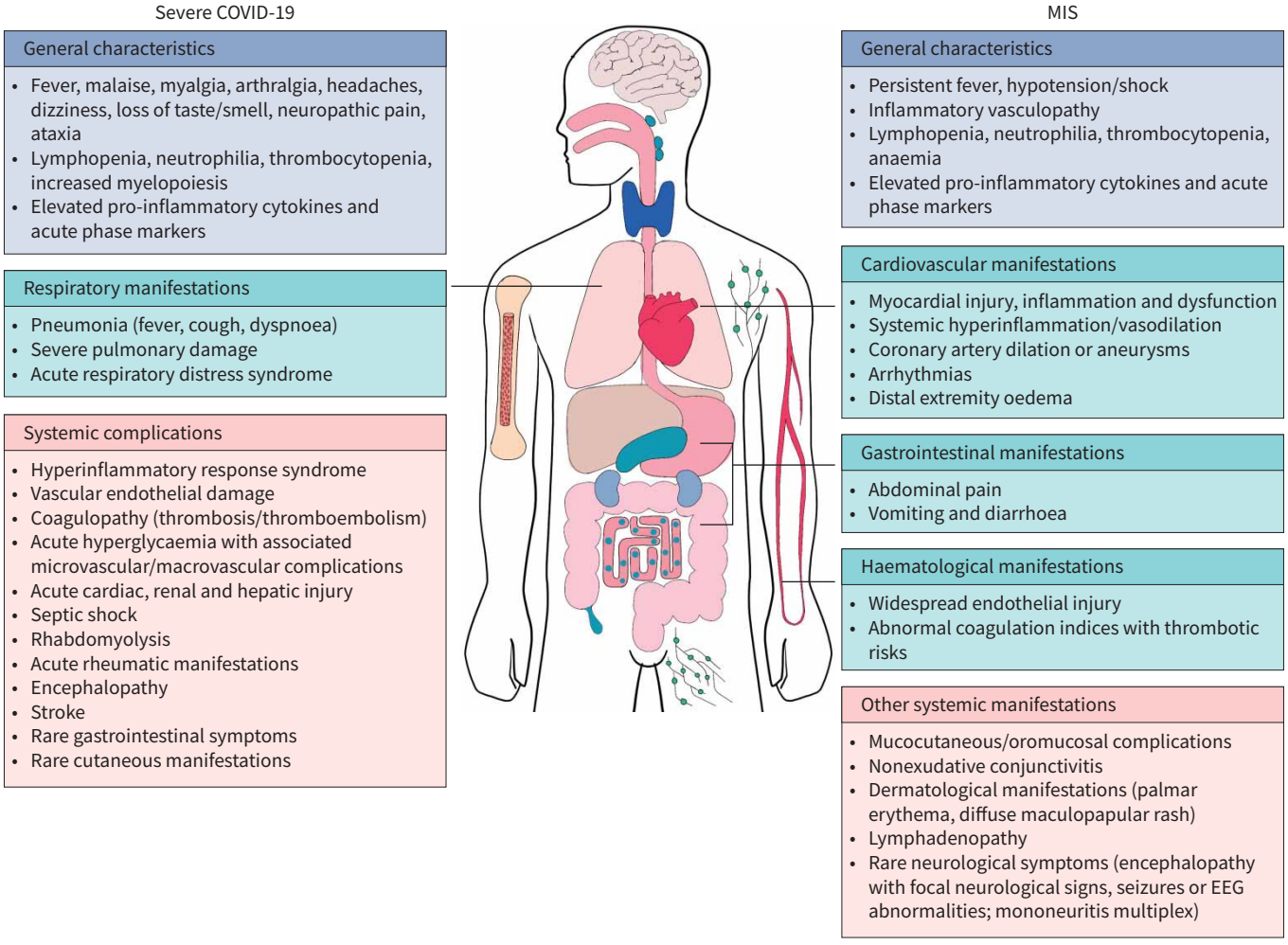

FIGURE 1 Pathological presentations of severe coronavirus disease 2019 (COVID-19) *versus* multisystem inflammatory syndrome (MIS). Severe COVID-19 is associated with pneumonia, significant pulmonary damage and respiratory distress, and subsequent systemic complications. MIS represents a febrile hyperinflammatory syndrome without severe respiratory illness but prominent cardiovascular, gastrointestinal and haematological perturbations, and other diffuse systemic manifestations with multisystem involvement. EEG: electroencephalogram.

has prominent cardiovascular, gastrointestinal and haematological involvement and manifests as a delayed response 2–12 weeks following SARS-CoV-2 infection [8, 48–52] (figure 1).

Immunopathogenesis of SARS-CoV-2-induced disease phenotypes

Mild–moderate COVID-19 and asymptomatic SARS-CoV-2 infection

In patients with mild–moderate COVID-19, there is an early, transient IFN-α wave in the circulation (but an absence of IFN-β) [26, 27], albeit with a degree of viral antagonism by SARS-CoV-2 [53–55]. Resultant antiviral protection is induced *via* the initiation of prompt and robust innate and adaptive antiviral mechanisms [23], leading to viral clearance and recovery (figure 2a).

A novel SARS-CoV-2 human challenge model, with a low inoculum dose, in healthy young adults (aged 18–29) without any known immune-modulating risk factors, was used to establish viral kinetics over the course of primary infection with SARS-CoV-2 [56]. Such human challenge models can generate critical information *via* the controlled investigation of pathogenesis, linking early antiviral responses and inflammatory responses to both viral replication and host genetics, identification of host factors associated with protection in those who resist or recover well from infection, as well as testing the efficacy of vaccines and therapeutics.

SARS-CoV-2 infection can also be asymptomatic, with similarities in immunodynamics to mild disease [57–60]. However, despite having no clinical symptoms and normal chest radiography imaging, some of

https://doi.org/10.1183/16000617.0197-2022

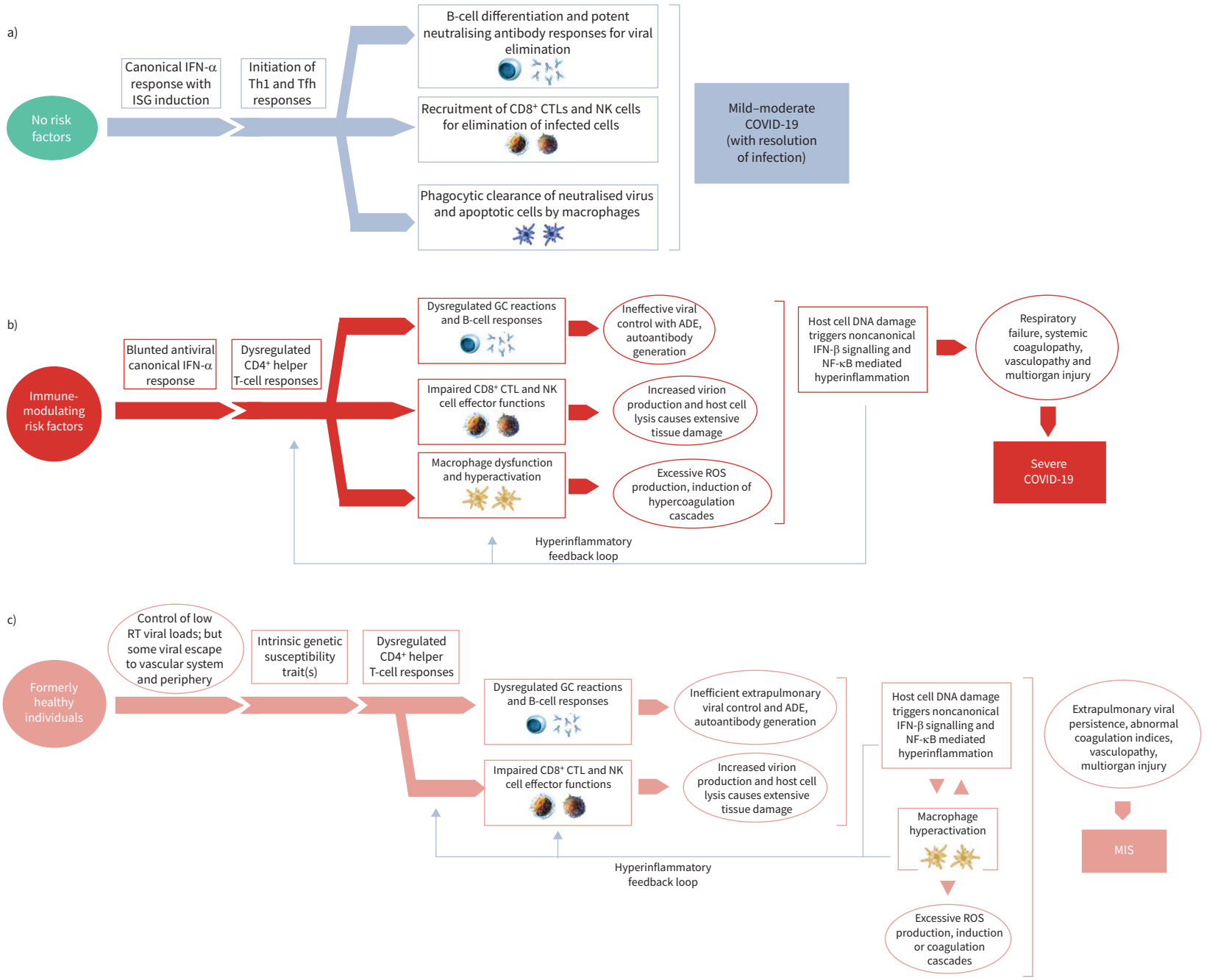

FIGURE 2 Proposed disease pathways implicated in the coronavirus disease 2019 (COVID-19) spectrum and multisystem inflammatory syndrome (MIS). a) *Mild–moderate COVID-19*. In individuals without any risk factors, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection induces local tissue damage, triggering canonical antiviral interferon-α (IFN-α), with subsequent induction of $CD4^+$ helper T-cell responses (T-helper 1 (Th1) and T follicular helper (Tfh)) that facilitate destruction of virally infected cells by $CD8^+$ cytotoxic T-lymphocytes (CTLs) and natural killer (NK) cells, promote antibody responses for neutralisation of SARS-CoV-2, and the phagocytic clearance of apoptotic cells and neutralised virus by macrophages, leading to viral clearance and recovery. b) *Severe COVID-19*. Associated with immune-modulating risk factors and characterised by a hallmark of blunted canonical IFN-α expression. Impaired Th1 and Tfh responses, suboptimal humoral responses that promote antibody-dependent enhancement (ADE), lymphocyte exhaustion and impaired functions, and macrophage dysfunction, permit further viral replication to cause extensive tissue damage. Sensing of self-DNA damage in infected host cells by the adaptor molecular STING (stimulator of IFN genes) can activate NF-κB-mediated hyperinflammatory noncanonical IFN-β signalling to induce extensive pro-inflammatory cytokine release that further dysregulates lymphoid and myeloid compartments without activating antiviral responses, whilst generating a hyperinflammatory feedback loop. Superantigenic stimulation can also skew helper T-cell responses and enhance pro-inflammatory cytokine release. Resultant dysregulated inflammatory pathology is linked to coagulopathy, vasculopathy, multiorgan injury and failure. c) *MIS*. Typically affects previously healthy individuals without pre-existing comorbidities. Patients exhibit absent/low respiratory tract (RT) viral loads and lack severe respiratory illness, which may be due to fewer infected RT cells, but may possess intrinsic genetic susceptibility traits that cause harmful maladaptations of adaptive responses and trigger the activation of systemic hyperinflammation pathways upon SARS-CoV-2 infection. Abnormal $CD4^+$ helper T-cell functions, dysregulated humoral responses and impaired lymphocyte cytolytic functions can potentiate viral spread to extrapulmonary tissues, activating hyperinflammatory pathways (*e.g.* STING-mediated late, noncanonical hyperinflammatory IFN-β signalling) to promote systemic autonomous loops of inflammation with hypercoagulation, vasculopathy and multiorgan involvement. GC: germinal centre; ISG: IFN-stimulated gene; ROS: reactive oxygen species.

these asymptomatic individuals display subclinical lung abnormalities with characteristic pulmonary ground glass opacification on computed tomography imaging [57] that is indicative of significant pulmonary inflammation and could therefore have long-term harmful implications. Indeed, there are reports of patients suffering with diverse, prolonged multisystem involvement, persistent symptoms and significant disability, without having recovered by up to 7 months post-infection [61, 62]. These post-COVID-19 sequelae arise from prolonged inflammation and coagulopathy and are often referred to as long COVID, which is independent of initial disease severity [63–67]. This suggests that inflammatory responses can be marked and persistent despite early viral clearance, hinting at a potentially indirect correlation between the effectiveness or potency of an initial antiviral response and the subsequent inflammatory response induced.

An early acute response with hyperinflammatory pathology: severe COVID-19

Immune-modulating risk factors associated with severe COVID-19

Severe COVID-19 is associated with impaired host antiviral mechanisms, persistent blood viral loads and a disproportionate systemic pro-inflammatory response. Individuals with chronic inflammatory processes, prothrombotic states, atherogenic profiles with a reduced cardiorespiratory reserve or predisposing genetic defects may be susceptible to fatal outcomes due to altered immune response states that compromise host antiviral immune response mechanisms and/or activate hyperinflammatory responses [1, 7, 18–20, 28, 68] (table 1). Age-related susceptibility has been indicated as a major risk factor contributing to COVID-19 severity. As a result of numerous age-related phenomena (*e.g.* increased ACE2 expression patterns, weakened antiviral IFN-1 responses, inflammaging, immunosenescence and comorbidities), elderly adults are at particularly high risk of developing severe disease that requires admission to intensive care units and implementation of mechanical ventilation, and have a higher mortality risk [2, 3, 69]. Conversely, the majority of children without comorbidities have a mild disease course or asymptomatic infection, likely due to a combination of several factors (*e.g.* lower tissue ACE2 and TMPRSS2 expression in children, higher availability of naïve T-cells that can respond to new infections, and "trained immunity" due to frequent exposure to common viral respiratory pathogens and/or childhood vaccinations) [25, 70]. However, severe cases and deaths have also been reported in children, with infants being most vulnerable to severe disease and accounting for the highest proportion of hospitalisation. This may be linked to transiently increased ACE2 expression at birth, combined with poor IFN-1 responses upon viral infection, altered T-helper type 1 (Th1) function and low expression of cytotoxic and inflammatory mediators in neonates [25, 71]. Increased severity and mortality rates in all ages are also linked to comorbidities with pro-inflammatory diathesis (*e.g.* chronic respiratory conditions, cancer, obesity, diabetes, cardiovascular disease, hypertension, chronic kidney disease, sickle cell disease and autoimmune diseases), an immunosuppressed status and high occupational viral exposure [5–7, 44, 72, 73], regardless of age. Many of these chronic diseases are associated with higher ACE2 expression in the lungs, as well as IFN-1 dysregulation and inefficient innate and adaptive responses, which negatively affect antiviral host mechanisms and the ability to respond to new infections [7, 18, 28, 74]. Other factors that can modify host

TABLE 1 Risk factors that affect host antiviral immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and increase susceptibility to severe coronavirus disease 2019 (COVID-19)

Risk factor	Altered physiological and immune profile
Age-related susceptibility: elderly people	• ACE2 expression in airway and alveolar epithelial cells increases with advancing age, affecting SARS-CoV-2 cellular entry and infection • Weakened antiviral IFN-1 responses upon viral infection • Inflammaging and counter-regulation of anti-inflammatory molecules may promote pro-inflammatory cytokine secretion, leading to a hyperinflammatory milieu that can cause widespread tissue damage • Immunosenescence and decreased naïve T-cells and B-cell numbers, with involution of primary lymphoid organs, lead to reduced ability of the host to respond to new infections, allowing increased viral loads, a hyperinflammatory status and disease progression • Apoptotic priming of lung tissue decreases with age, which may lead to increased virion production due to later apoptosis induction in infected cells • Comorbidities/chronic diseases are more common with advancing age, further contributing to the enhancement of COVID-19 severity and risk of mortality
Age-related susceptibility: neonates	• Increased ACE2 expression at birth (which subsequently drops and then gradually increases with time) makes infants more susceptible to infection • Low expression of cytotoxic and inflammatory mediators after birth, with inefficient clearance of virally infected cells by CTLs and NK cells • Altered early Th1 functions (skewed towards a Th2 profile) leads to insufficient antiviral responses
Comorbidities and chronic diseases[#], an immunosuppressed status, high viral exposure	• Altered immune statuses that impair host defence mechanisms can result in inability to produce effective/timely antiviral responses, leading to higher viral loads, a hyperinflammatory status and disease progression • Excessive tissue damage can trigger abnormal macrophage activation, leading to uncontrolled pro-inflammatory cytokine release with associated coagulopathy, vasculopathy and multiorgan injury • Altered atherogenic profiles may augment coagulopathy in COVID-19 • Increased tissue expression of ACE2 in several comorbidities/chronic diseases or resulting from treatment of chronic diseases (*e.g.* COPD, hypertension, diabetes, carcinomas and cardiac diseases) • Increased tissue expression of TMPRSS2 in COPD and hypertension
Biological sex (male) bias	• The ACE gene is located on the X-chromosome and is downregulated by oestrogen, and higher ACE2 expression in male compared to female lungs, which may lead to higher infection rates in males • Steroid hormones affect immune cell functions: variability of hormone expression may be implicated in the variability of immune responses and age-related sex dimorphism
Pregnancy	• Strong Th1 response during implantation and placentation, followed by Th2 dominance and another Th1 wave at parturition/postpartum: gestational age-dependent dynamic immune status may promote development of severe COVID-19 due to increased pro-inflammatory cytokine production or Th1 response counteraction, or obstetric complications with adverse effects on maternal and fetal health • Pregnancy is a prothrombotic state due to increased oestrogen levels and altered immune responses, and may augment coagulopathy in COVID-19
ABO blood group	• Circulating anti-A antibodies (possessed by blood group O, absent in group A) interfere with virus-cell adhesion: blood group A at higher risk of SARS-CoV-2 infection • A-allele (possessed by blood group A) associated with a higher risk of cardiovascular disease and lower expression of factors that promote coagulation by blood group O (protection from complications associated with severe COVID-19 in blood group O)
Genetic susceptibility and environmental factors	• Several genetic factors relating to key host antiviral defence mechanisms or mediators of inflammatory organ damage have been proposed and/or identified to influence susceptibility and severity, including IFN-1 signalling pathway dysfunction, other cytokine defects/polymorphisms, errors of the ACE2 gene, HLA locus, TLR and complement pathways, and myeloid compartments • Race and ethnicity may have genetic influences, but could also have major environmental factors underlying predisposition

[#]: *e.g.* obesity, hypertension, diabetes, cancer, respiratory, cardiovascular or autoimmune diseases. ACE2: angiotensin converting enzyme 2; CTL: cytotoxic T-lymphocyte; HLA: human leukocyte antigen; IFN-1: interferon 1; NK: natural killer; Th: T-helper cell; TLR: Toll-like receptor; TMPRSS2: transmembrane protease serine 2.

responses to infection include biological sex, pregnancy, certain ABO blood group antigens, as well as genetic variability [2, 4, 68, 75–77] (table 1). SARS-CoV-2 infection thus unmasks the host impairment of key antiviral defence mechanisms and altered regulation of inflammatory responses that would have otherwise been silent in many of these patients, emphasising the multifactorial causes of severe COVID-19. In this regard, SARS-CoV-2 appears to be particularly adept at revealing these traits, which

have not been apparent following other infections, possibly due to the vast and accelerated spread of SARS-CoV-2 infection on a global scale within a very short time-frame.

Impaired host innate mechanisms in severe COVID-19

Impaired early IFN-1 signalling is a hallmark of severe COVID-19 and is associated with lower viral clearance. Low or no IFN-α response typically precedes clinical deterioration and transfer to intensive care units, characterising the most severe or critical cases requiring invasive ventilation, with a significant reduction in mean expression of six ISGs defining an IFN-1 signature, compared to mild–moderate disease with high IFN-α levels [26, 78]. Self-renewing tissue-resident alveolar macrophages (AMs), located within the airspace lumen in the lungs, provide the first line of defence against respiratory pathogens entering the respiratory system and, along with lung-resident plasmacytoid DCs (pDCs), produce large amounts of antiviral IFN-1α [79–81]. However, direct SARS-CoV-2 infection of AMs (as well as circulating blood monocytes) has been demonstrated [82–85]. While early *in vitro* studies suggest that SARS-CoV-2 infection of AMs may be abortive [86], subsequent *in vivo* studies indicate that infected AMs may be able to support SARS-CoV-2 viral replication, contingent on their polarisation [82, 83]. It is therefore possible that SARS-CoV-2 infection of pro-inflammatory AMs may actively facilitate viral spread, while the opposite might be true for alternatively activated AMs [83]. Notably, recent *post mortem* studies suggest that AMs are not a significant source of viral replication in the alveolus as they lack the receptors to support viral entry [39], while other studies have reported evidence that is indicative of viral replication in AMs in humanised mice or AMs in patients with severe SARS-CoV-2 [82, 87]. Differential ACE2 expression may explain these differences, which could be influenced by macrophage polarisation. The loss of tissue-resident AMs and recruitment of monocyte-derived inflammatory macrophages have been observed in *post mortem* lungs and humanised mouse models of COVID-19 [39, 87]. However, *post mortem* studies also suggest that pulmonary inflammation does not always directly correspond to the level of viral presence in the respiratory epithelium [88], indicating the presence of autonomous inflammatory circuits even following local viral clearance in the lung and viral translocation to other sites at the time of death. Indeed, there are reports of pyroptotic cell death of monocytes and AMs following antibody-mediated SARS-CoV-2 uptake, which contributes to the systemic hyperinflammation in severe COVID-19 [85]. Notably, IFN-1 antagonism, by SARS-CoV-2 proteins, in reprogrammed pro-inflammatory AMs found prevalently in the lungs of severely affected patients, as well as pyroptotic or apoptotic death of these resident AMs, can result in an impaired IFN-1 response [79, 89, 90]. Furthermore, pDCs, activated by the virus without productive infection [91], demonstrate diminished IFN-α production in severe COVID-19 [27]. Additional reports of IFN-1 dysregulation describe genetic errors that impede IFN-1 immunity [92, 93], autoantibodies that bind and functionally neutralise almost all IFN-1s [94, 95], as well as sustained abrogation of antiviral IFN-1 production [78], in patients with life-threatening COVID-19 compared to mild cases or asymptomatic subjects. IFN-1 dysregulation in severe COVID-19 thus occurs through a combination of different impaired host antiviral mechanisms and viral antagonism of IFN-1 induction [28, 31, 53, 55] . Further studies are needed, however, to define the exact cell types in which antiviral responses are defective, the roles of specific cell death paradigms in impairing these responses and the relative contributions of genetic factors and autoimmunity to impaired IFN-1 antiviral responses.

Aberrant IFN-1 responses have been further linked to a second wave of inflammatory cytokine release and the expression of factors that promote pulmonary intravascular coagulopathy and fibrin-based blood clots [96, 97], and a high incidence of multiorgan thrombosis is linked to severe COVID-19 with respiratory failure [98–101]. Excessive cytokine release may promote a hypercoagulable state by inducing endothelial dysfunction, the activation and aggregation of platelets with high thrombogenic capacity, as well as abnormal neutrophil activation, to promote tissue damage, vascular injury and immunothrombosis [102–106]. Endothelial cell activation affects vessel integrity, triggering the release of factors that increase platelet activation and adhesion, generating a procoagulative state [35]. Damaged endothelial cells can promote neutrophil activation and neutrophil extracellular trap (NET) formation [107]. NETs can trigger microvascular thrombosis, which is implicated in COVID-19-related ARDS, multiorgan dysfunction and death [104–106]. Antiphospholipid autoantibodies can also promote thrombosis in vascular beds through neutrophil, endothelial cell and platelet activation [108]. Activated platelets release platelet factor 4 (PF4), while activated endothelial cells release polyanionic proteoglycans (PGs), to form PF4-PG complexes, which can expose PF4 immunogenic epitopes to activate extrafollicular B-cells that secrete PF4 autoantibodies. The subsequent binding of PF4 autoantibodies to PF4-PG immune complexes on platelets and endothelial cells may stimulate their pro-coagulative activities [109]. Platelet activation can instigate their consumption by scavenging macrophages, leading to thrombocytopenia. The combination of thrombocytopenia and thromboembolic complications is associated with critical COVID-19 and increased mortality [110]. Autoantibodies targeting IFN-1s, antiphospholipids, PF4, as well as natural killer (NK)

cells, $CD8^+$ cytotoxic T-lymphocytes (CTLs), B-cells and macrophage-expressed proteins, have been associated with increasing COVID-19 severity [94, 95, 108, 111, 112]. Autoantibody production is typically genetically predetermined and can therefore shape clinical presentation following infection [113]. Further studies should correlate the level of these responses to COVID-19 severity.

Impaired host adaptive mechanisms in severe COVID-19

Canonical IFN-1 signalling contributes to the differentiation of T follicular helper (Tfh) cells, which are critical for germinal centre (GC) reactions, during which B-cells undergo developmental changes and acquire memory [31]. Severe COVID-19 cases exhibit defective Bcl-6^+ Tfh cell differentiation and do not develop the lymph node and splenic GCs required for durable antiviral responses [24]. Abnormal Tfh cell differentiation may lead to extrafollicular B-cell activation in critically ill patients [114], with greater antibody titres corresponding to increasing COVID-19 severity and a pathogenic antibody response [114, 115]. This may be through antibody-dependent enhancement (ADE), whereby absent or sub-neutralising antibody concentrations relative to viral load (potentially due to impaired GC reactions) fail to neutralise SARS-CoV-2, thereby permitting virus–antibody complexes to bind to phagocyte Fcγ receptors (FcγRs) to enable viral uptake, replication and a rapidly increasing viral load [24, 85, 114–116]. However, while the FcγR-mediated uptake of antibody-coated SARS-CoV-2 by monocytes and macrophages triggers their pyroptotic death, thereby aborting viral replication, it nevertheless promotes systemic hyperinflammation, which contributes to acute lung injury, multiorgan damage, vascular leak and respiratory distress [85]. ADE might occur alone or in combination with impaired cellular responses [114, 117] that are associated with various risk factors (table 1).

Lymphocyte cytotoxic effector functions play protective roles that are critical for resolution of SARS-CoV-2 infection [26, 118, 119] and $CD8^+$ CTLs may compensate for aberrant humoral immunity in COVID-19 [120–122]. However, functional exhaustion of CTLs and NK cells (while NK cells classically form part of the innate response, adaptive characteristics of NK cells following infection have been identified over the past decade), impaired lymphocyte cytotoxic capacity and progressive lymphopenia correlate with increasing disease severity and increased levels of circulating pro-inflammatory cytokine levels in SARS-CoV-2 infection [123, 124]. Pro-inflammatory cytokines can promote the functional exhaustion of NK cells, inhibiting their cytotoxicity, whilst simultaneously enhancing neutrophil infiltration and activity [125–128]. The S glycoprotein can also directly suppress NK cell killing *via* crosstalk with infected lung epithelial cells [129]. Finally, since IFN-1 signalling promotes CTL and NK cell effector functions [130–132], aberrant canonical IFN-1 signalling with inadequate induction of lymphocyte cytotoxic functions may promote inflammatory pathogenesis through ineffective viral clearance.

Innate-adaptive crosstalk in severe COVID-19

Impaired lymphocyte effector functions can promote viral spread within the body, thereby enhancing pathogenic inflammation. Damaged DNA released from infected host cells can be recognised by the adaptor molecule, STING (stimulator of IFN genes), which activates antiviral IFN regulatory factor 3 (IRF3) and/or inflammatory NF-κB pathways, terminating with IFN-1 induction. However, DNA release following SARS-CoV-2 infection activates NF-κB but not the antiviral IRF3 system, leading to exaggerated production of NF-κB-mediated cytokines, which may lead to the paradoxical upregualtion of ISGs in severe COVID-19 [133–135]. This noncanonical IFN-1 signalling later in the disease pathway represents an alternative pathway of response (in particular, it results in IFN-β expression, which is absent from all patients in early SARS-CoV-2 infection), and can result in inappropriate hyperinflammatory signalling without effective resolution of infection [26, 133, 136–139].

Pro-inflammatory cytokines can suppress lymphopoiesis while inducing myelopoiesis [140] and sustained release can lead to abnormal macrophage activation [97, 141–143]. Evidence of emergency myelopoiesis with production of excessive reactive oxygen species (ROS)- and nitric oxide synthase (NOS)-expressing myeloid cells has been implicated in severe COVID-19 with respiratory failure [141, 143, 144]. Key features include greater percentages of highly inflammatory monocyte and macrophage populations in peripheral blood and bronchoalveolar lavage fluid, markedly decreased HLA-DR (human leukocyte antigen–DR isotype; responsible for antigen presentation to T-cells) expression in $CD14^+$ monocytes and lesions of histiocytic hyperplasia with haemophagocytosis and acute alveolar damage [141, 142, 144, 145]. Death of classically activated tissue-resident AMs can be triggered upon SARS-CoV-2 infection and there is recruitment of pro-inflammatory monocytes into the lungs and their transformation into pathogenic hyperinflammatory hyperferritinemic macrophages in patients with severe SARS-CoV-2 pneumonia [82, 145]. This altered macrophage composition within the alveolar compartment contributes to a detrimental loop of pro-inflammatory cytokine release, with a shift towards excessive ROS generation to cause widespread oxidative stress and tissue damage [79, 97, 145, 146]. Dysregulated macrophage activation is

therefore a key contributor to the hyperinflammatory status in severe COVID-19. However, viral replication in the alveolar compartment appears to be limited to rare AT2 cells; and thus the promotion of inflammation by AMs may be more contingent on SARS-CoV-2 virions translocating to the alveoli from the upper airways, followed by endocytosis of virions/virally infected cells, driving the induction of specific pro-inflammatory phenotypes that can promote subsequent systemic responses [39]. Furthermore, any viral replication within the lungs could lead to increased infiltration of inflammatory immune cells [82, 147, 148]. Indeed, while the exact origin of the virus-promoting response has been debated, SARS-CoV-2-infected AMs produce T-cell chemoattractants, and upon recruitment and activation, T-cells induce inflammatory cytokine release from macrophages and further promote T-cell activation to form a positive feedback loop that drives persistent inflammation and tissue injury [82].

Notably, a late and persistent noncanonical IFN-1 response may further promote the infiltration of pathogenic hyperinflammatory monocyte-derived macrophages that replace tissue-resident AMs in the lungs, thereby enhancing lung immunopathology, vascular leakage and immune cell dysfunction [30, 32]. However, some studies have reported that, in patients with severe SARS-CoV-2 pneumonia, IFN-1 expression by cells in the alveolar compartment was not detected later in the clinical course [82], suggesting that the hyperinflammatory response may be generated systemically. Reasons for these differences in origin of responses remain unclear. Nevertheless, an IFN-1-associated prothrombotic neutrophil hyperinflammatory signature has been identified in COVID-19 ARDS [148]. As such, it appears as though severe COVID-19 cases lack early, mucosal, canonical (classical) antiviral IFN-1 signalling, leading to insufficient antiviral host immune responses and persistence of viral loads [26]. However, later on, a systemic, noncanonical IFN-1 pathway can be triggered to promote NF-κB-mediated hyperinflammation with uncontrolled pathogenic pro-inflammatory cytokine release that augments the dysregulation of host antiviral functional responses, whilst causing widespread tissue damage, coagulopathy and vasculopathy [133, 137, 149, 150] (figure 2b). The complications associated with severe COVID-19 may therefore be strongly related to prolonged exposure to circulating pathogenic inflammatory cytokines [82] and may become independent of viral replication, as we and others have suggested [39, 40].

Delayed acute systemic hyperinflammatory response: MIS

There is significant overlap of the immune perturbations in MIS with those observed in severe COVID-19, including impaired antigen presentation, abnormal B-cell and $CD4^+$ T-cell responses, dysregulated cytotoxic lymphocyte effector functions with evidence of exhausted CTL and downregulated NK cell signatures, and hyperinflammatory macrophage activity [151–159] (figure 2c). However, the signatures of these two conditions illustrate dysregulation of inflammatory and antiviral immune defence mechanisms with distinct temporal patterns [9, 160]. While COVID-19 symptoms develop within a median of 6.57 days after viral exposure (with slightly shorter incubation with Omicron variants) and progress over the following week in severe disease [161, 162], MIS is diagnosed 2–12 weeks following initial SARS-CoV-2 infection, with accelerated progress to critical status [163]. MIS patients often demonstrate negative SARS-CoV-2 reverse-transcriptase PCR results with positive SARS-CoV-2 serology. A positive test result for SARS-CoV-2 infection within the preceding 12 weeks of presentation with severe illness requiring hospitalisation and laboratory evidence of severe inflammation [8–10] indicates a delayed hyperinflammatory response several weeks after initial asymptomatic/mild SARS-CoV-2 infection. MIS patients exhibit prominent systemic features with cardiovascular, gastrointestinal and haematological clinical manifestations whilst lacking severe localised respiratory illness and present with systemic disease and significant extrapulmonary organ dysfunction [8, 9, 49, 52, 156] (figure 1).

MIS patients often exhibit a lack of, or minimal, respiratory tract viral loads [8, 10] and develop a delayed immune activation syndrome driven by persistent antigen presence, with widespread viral persistence in extrapulmonary tissues [164]. In paediatric patients that develop MIS-C, the lack of severe respiratory illness could be attributed to fewer infected cells in the respiratory tract, due to lower ACE2 expression in the lungs in children [25, 157, 165, 166]. By extrapolation of the available evidence [8, 52, 160, 167], it is possible that initial low respiratory tract viral loads, and therefore lower immune activation, could explain the scarcity of severe pulmonary symptoms in MIS-A. Lower levels of cell lysis and release of virions may induce a sufficient antiviral host response to limit pulmonary disease [157] in both paediatric and adult cases. However, the inability of the host to achieve complete viral clearance from the respiratory tract [164] may allow extrapulmonary viral spread *via* the vascular system in predisposed individuals [156, 168, 169]. There is also evidence of direct SARS-CoV-2 infection of the vascular endothelium [38]. Furthermore, increased markers of immune cell activation and egress to the periphery have been identified in MIS-C patients [156], which may be accompanying viral migration and could contribute to the delayed post-infectious immune dysregulation in MIS. Since MIS was initially described in children, studies investigating its pathophysiology have largely focussed on MIS-C and therefore much of the evidence we

provide here is based on studies investigating MIS-C. However, there appear to be no clear differences in case definitions of MIS in children and adults [8, 10, 170], likely indicating the same disease entity.

While the vast majority of healthy individuals without any pre-existing comorbidities have a mild COVID-19 disease course, we propose that healthy subjects possessing (to date, unidentified) intrinsic genetic susceptibility traits that trigger harmful maladaptations of key adaptive immune responses to SARS-CoV-2 infection may develop MIS. The resultant abnormal immune responses may permit viral spread to extrapulmonary tissues and promote systemic hyperinflammatory responses, driving MIS pathogenesis (figure 2c). This speculation is supported by several lines of evidence (albeit predominantly from small studies that may require further validation), including 1) dysregulation of several adaptive response pathways in MIS patients, 2) the autoimmune disease phenotype of MIS, 3) potential SARS-CoV-2 superantigenic activity being a contributor to its development, 4) the likely genetic components in the aetiology of hyperinflammatory syndromes such as Kawasaki disease (KD), with which MIS shares many features, and 5) the presence of vascular patrolling CTLs in MIS patients, which have previously been linked to inflammatory conditions with cardiovascular damage.

Dysregulation of various mechanisms that interfere with adaptive immune compartments have been described in MIS patients. These include abnormal $CD4^+$ helper T-cell, cytotoxic lymphocyte and B-cell responses, which may promote viral spread and persistent antigen presence and lead to ADE, thereby prolonging inflammation [151–157, 164]. Furthermore, it is possible that self-DNA release from SARS-CoV-2-infected host cells could cause a STING-mediated late, noncanonical IFN-β response as seen in severe COVID-19 and KD [134, 137, 169] that leads to hypercoagulation, vasculopathy, multiorgan involvement and injury. Antigen-presenting cells responsible for antiviral IFN-1 production demonstrated augmented levels of phospho-signal transducer and activator of transcription 3 in MIS-C, which may be indicative of noncanonical IFN-1 signalling that can restrain antiviral responses [156, 171, 172]. Additional reports of sustained NF-κB and tumour necrosis factor-α activation, myocardial infiltration of hyperinflammatory macrophages and increased neutrophil activation in MIS-C patients with severe myocarditis [173] further support the likelihood of a late noncanonical hyperinflammatory IFN-1 response with subsequent NF-κB-mediated inflammatory pathogenesis in these patients [133, 134]. The immune dysregulation in MIS is therefore comparable to severe COVID-19, although the timing and localisation presentation represent a different disease phenotype with a delayed and systemic nature (figures 1 and 2).

MIS-C has been characterised as having an autoimmune disease phenotype with dysregulated B-cell responses and autoantibody production. This can lead to enhanced neutrophil activation and augmentation of complement and coagulation pathways, which are implicated in several systemic, autoimmune and inflammatory vascular diseases [174]. Multiple autoantibodies targeting endothelial cells, the gastrointestinal tract and immune mediators that implicate organ systems central to MIS-C pathology have been linked to its pathogenesis [152, 156] and autoantibody generation is often genetically predetermined [113]. These autoantibodies may trigger extensive immune complex formation that cannot be quickly eliminated [156]. Once deposited in tissues and perivascular spaces, these immune complexes may be capable of causing widespread inflammatory injury and vascular permeability *via* complement activation, Fc receptor-mediated responses and cytokine network dysregulation [169].

SARS-CoV-2 superantigenic activity, with the capacity to induce autoimmune pathways, has been indicated as another contributor to the development of MIS-C [175–177], representing a further pathomechanism that is shared with severe COVID-19. Superantigen-reactive hyperinflammatory $CD4^+$ Th cells can promote macrophage hyperactivation to induce relentless pro-inflammatory cytokine secretion [169, 178]. Additional MIS manifestations such as conjunctivitis, oedema, rash and fever are symptoms observed in the context of superantigen-mediated responses, subsequent to elevated cytokine release [179, 180].

Hyperinflammatory syndromes mainly occur in genetically susceptible individuals, as demonstrated for the paediatric febrile vasculitis syndrome, KD, which is commonly associated with post-infectious epidemiology and with which MIS shares several resemblances [180, 181]. Indeed, it has been suggested that MIS-C could be a new presentation of KD that is triggered by SARS-CoV-2 infection [182], despite certain prominent differences between classical KD and MIS [151, 152, 156]. Furthermore, a few recent studies have suggested that rare genetic variants could be potential contributors to MIS pathogenesis, although larger studies would be required to interrogate and corroborate these findings [182–185].

Finally, vascular patrolling $CX3CR1^+$ CTLs (associated with increased cardiovascular disease risk and implicated in inflammatory conditions with vascular damage) [186, 187] have been identified in MIS-C [164]. Since the hyperinflammatory response in MIS involves endothelial cell activation and associated

coagulopathy, we presume the presence of the vascular patrolling CTLs to be secondary to endothelial cell activation, which we speculate may occur both directly as a result of SARS-CoV-2-mediated effects on the vascular endothelium [38], as well as a secondary response to systemic hyperinflammation [188]. The localisation of immune cells to the vascular endothelium is an important step in atherogenesis [186] and there is further evidence of endothelial injury and coronary artery immune cell infiltrates in pathological samples from MIS-C patients [180, 188]. Nonetheless, the precise mechanisms responsible for the spatiotemporal control of immune responses in MIS remain elusive and this topic requires further investigation.

Aetiology and immunological evolution of severe COVID-19 *versus* MIS

There appears to be a continuum of immune dysregulation across the COVID-19 spectrum and MIS, varying in extent, timing and localisation, but severity of COVID-19 or the development of MIS is dependent on a range of unique aetiological factors that can result in variable efficacy of host responses to infection. An early hyperinflammatory response with significant respiratory manifestations differentiates severe COVID-19 from MIS, the latter being a delayed hyperinflammatory response with pronounced systemic manifestations, but no significant respiratory illness (figures 1 and 2). COVID-19 and MIS therefore represent distinct disease phenotypes, with distinct spatiotemporal adaptations (figure 3). Severe COVID-19, associated with immune-modulating risk factors that affect host antiviral immune mechanisms [1, 2, 4–6] (table 1), is a consequence of perturbations in the primary innate response to infection, with further disruption of downstream innate and adaptive antiviral mechanisms that promote dysregulated

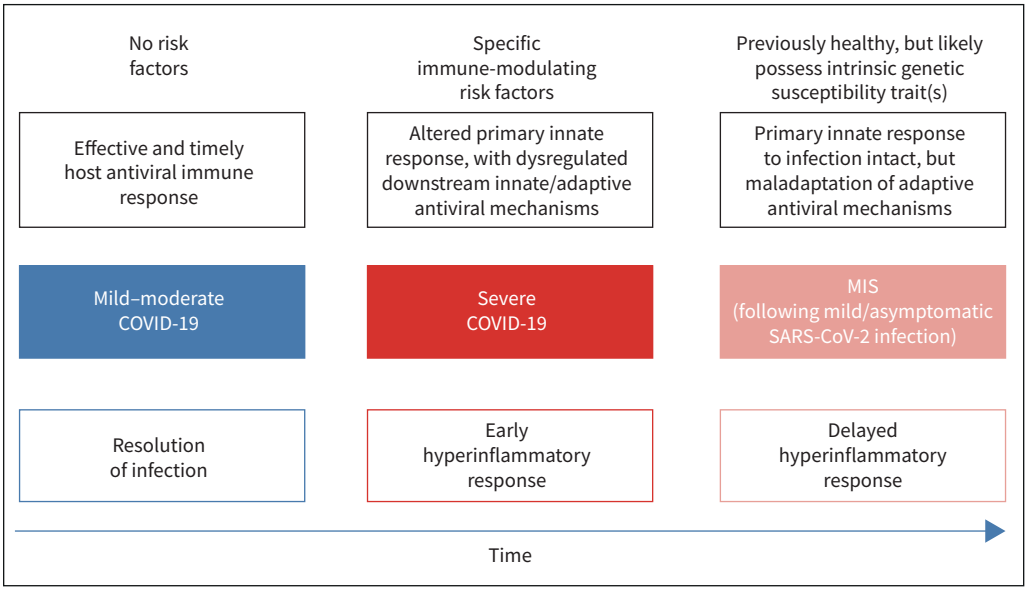

FIGURE 3 Distinct spatiotemporal adaptations of the coronavirus disease 2019 (COVID-19) spectrum and multisystem inflammatory syndrome (MIS). In mild–moderate COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection often does not progress beyond the respiratory tract, and viral clearance is achieved within 2–14 days, due to effective antiviral host defence mechanisms. Severe COVID-19 is an early acute hyperinflammatory response that develops within 1 week of exposure and develops due to impairment of primary innate response to infection (blunted canonical interferon (IFN)-α response) and weakened downstream innate and adaptive antiviral mechanisms that promote dysregulated inflammatory responses (*e.g.* late noncanonical IFN-1 signalling with NF-κB-mediated inflammatory pathogenesis), resulting in significant respiratory and systemic manifestations. It primarily affects the respiratory tract to cause significant pulmonary injury, but also has diffuse systemic involvement. Conversely, MIS typically affects previously healthy individuals without any comorbidities and is a delayed acute hyperinflammatory response with prominent systemic manifestations, but minimal/no respiratory illness, presenting 2–12 weeks post-infection. Primary innate response to infection is not impaired in MIS, but affected individuals likely possess genetic susceptibility trait(s) that cause harmful maladaptations of adaptive response pathways, promoting extrapulmonary viral spread *via* the vascular system. This may lead to activation of systemic autonomous inflammatory loops (with late noncanonical hyperinflammatory IFN-β signalling) to drive pathogenesis.

inflammatory responses [26, 27, 133, 138, 139]. Conversely, MIS typically affects previously healthy individuals without any comorbidities [8]. It is possible that patients who develop MIS may have fewer infected respiratory tract cells (reflected in the diminutive/absent respiratory tract viral loads and lack of severe respiratory illness in these patients) [157, 169]. Primary innate response to infection is not impaired in MIS, but affected individuals most likely possess one or more intrinsic genetic susceptibility traits that remain inactive until triggered by SARS-CoV-2 infection [182] to cause harmful maladaptations of adaptive immune responses [151–157, 164]. This may potentiate viral translocation to extrapulmonary tissues *via* the vascular system, followed by activation of systemic autonomous hyperinflammatory loops to drive pathogenesis [133, 134, 156, 173] (figure 3).

Currently, a case-by-case approach is necessary for the management of both diseases. Generally, while glucocorticoids are used in both severe COVID-19 and MIS patients, high-risk patients can receive outpatient treatment with oral antivirals such as paxlovid, molnupiravir or intravenous remdesivir early after infection, while remdesivir (with or without dexamethasone and baricitinib) can be administered in hospitalised patients or those with hypoxemia [189–195]. This reflects the fact that epidemiological factors allow identification of high-risk patients and the rationale for interrupting earlier stages of viral replication is better established. Improved comprehension of the immunopathogenic pathways underpinning severe COVID-19 and MIS (caused by their respective unique etiological factors) may thus help to further stratify patients for more targeted treatment strategies. For example, identifying high-risk patients with mild–moderate disease, who have been hospitalised for a reason other than COVID-19, but may be at risk of moderate–severe lung disease and might benefit from treatment with monoclonal antibodies [78, 162]. For later presentations, anti-inflammatory agents (*e.g.* tocilizumab or baricitinib) are well established [196–198] and further stratification may allow selection of patients requiring treatment with various other immunomodulatory agents at later stages of disease. In MIS patients, anti-inflammatory strategies can be used, although with some differences, and intravenous immunoglobulin and thromboprophylaxis with low-dose aspirin is also considered [199–205]. Combinations of more directed anti-inflammatory and immunosuppressive therapies may also be beneficial for the treatment of MIS, given its autoimmune-like immunopathology.

Conclusion

Severe COVID-19 and MIS have distinct spatiotemporal profiles while sharing several immunological characteristics. The defects in host antiviral immune competence in both can contribute to dysregulated functional immune mechanisms and induce sustained hyperinflammation, coagulopathy, vasculopathy and multiorgan involvement. Given the epidemiological/aetiological factors underpinning the variable efficacy of host responses to infection and the timeline of events in the development of severe COVID-19 *versus* MIS, it will be important to determine the likely intrinsic defects in antiviral immunity against SARS-CoV-2 in populations at high risk of developing severe COVID-19 or MIS. It would also be important to establish whether vaccination can correct for any intrinsic defects in antiviral immunity against SARS-CoV-2 in some of these populations or whether the features of susceptibility persist in all high-risk groups despite vaccination, since some groups with altered immune profiles (*e.g.* those with an immunosuppressed status, obese subjects or the older population) have been shown to generate less effective responses to vaccination. A comprehensive understanding of the immunopathogenic pathways of severe COVID-19 and MIS, dictated by their respective aetiologies, can therefore enable the identification of superior targeted therapies and anti-inflammatory approaches that induce the most effective antiviral immune responses, as well as the development of improved vaccination strategies.

Points for clinical practice

- Severe COVID-19 and MIS have distinct spatiotemporal profiles while sharing several clinical characteristics (including hyperinflammation, hypercoagulability, vasculopathy and severe multiorgan dysfunction).
- Severe COVID-19 represents an early acute hyperinflammatory response to SARS-CoV-2 infection that develops within 1 week of viral exposure and is associated with several immune-modulating risk-factors including older age, noncommunicable chronic diseases, immunosuppression and pregnancy, among others.
- Severe COVID-19 is associated with pneumonia, significant pulmonary damage and respiratory distress, and subsequent systemic complications.
- Identification of high-risk patients with mild–moderate disease who have been hospitalised for a reason other than COVID-19 but may be at risk of severe pulmonary complications, may benefit from monoclonal antibody treatment and, for later presentations, patient stratification may allow selection of patients who might benefit from treatment with various other immunomodulatory agents.
- MIS represents a delayed acute hyperinflammatory response to SARS-CoV-2 infection that develops 2–12 weeks following initial SARS-CoV-2 infection in previously healthy individuals who may be genetically predisposed.

- MIS is a febrile hyperinflammatory syndrome without severe respiratory illness but prominent cardiovascular, gastrointestinal and haematological perturbations, and other diffuse systemic manifestations with multisystem involvement and an autoimmune-like immunopathological signature.
- In MIS patients, directed anti-inflammatory and immunosuppressive therapies may be beneficial for the treatment of MIS, given its autoimmune-like immunopathology.

Questions for future research

- Who is at high risk of developing long COVID-19 and why is it independent of initial disease severity?
- What are the likely intrinsic defects in antiviral immunity against SARS-CoV-2 in populations at high risk of developing severe COVID-19 or MIS? Are there any characteristic differences between different susceptible demographic groups?
- Can vaccination correct for intrinsic defects in antiviral immunity against SARS-CoV-2 in at least some of the populations at high risk of developing severe COVID-19?
- What are the specific contributory genetic risk factors implicated in MIS development?
- Can vaccination correct for intrinsic defects in antiviral immunity against SARS-CoV-2 in populations at high risk of developing MIS?

Provenance: Submitted article, peer reviewed.

Acknowledgements: We are grateful to the members of the COVID-19 Disease Map project, a large-scale community effort to describe SARS-CoV-2 virus–host interaction mechanisms, and this review was prepared with a motivation to support this project.

Author contributions: R. Fraser, A. Orta-Resendiz and A. Mazein developed the scope and focus of the review. R. Fraser wrote the article and prepared the figures and table. R. Fraser, A. Orta-Resendiz, D. Dockrell, M. Müller-Trutwin and A. Mazein critically appraised, revised and prepared the final version.

Conflict of interests: The authors declare no competing interests.

Support statement: A. Orta-Resendiz was supported by a doctoral fellowship from the University of Paris-Cité.

References

1 Brodin P. Immune determinants of COVID-19 disease presentation and severity. *Nat Med* 2021; 27: 28–33.
2 Salimi S, Hamlyn JM. COVID-19 and crosstalk with the hallmarks of aging. *J Gerontol A Biol Sci Med Sci* 2020; 75: e34–e41.
3 Rydyznski Moderbacher C, Ramirez SI, Dan JM, *et al.* Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. *Cell* 2020; 183: 996–1012.e1019.
4 Scully EP, Haverfield J, Ursin RL, *et al.* Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nat Rev Immunol* 2020; 20: 442–447.
5 Guan WJ, Liang WH, Zhao Y, *et al.* Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020; 55: 2000547.
6 Suárez-García I, Perales-Fraile I, González-García A, *et al.* In-hospital mortality among immunosuppressed patients with COVID-19: analysis from a national cohort in Spain. *PLoS ONE* 2021; 16: e0255524.
7 Radzikowska U, Ding M, Tan G, *et al.* Distribution of ACE2, CD147, CD26, and other SARS-CoV-2 associated molecules in tissues and immune cells in health and in asthma, COPD, obesity, hypertension, and COVID-19 risk factors. *Allergy* 2020; 75: 2829–2845.
8 Vogel TP, Top KA, Karatzios C, *et al.* Multisystem inflammatory syndrome in children and adults (MIS-C/A): case definition & guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2021; 39: 3037–3049.
9 Weatherhead JE, Clark E, Vogel TP, *et al.* Inflammatory syndromes associated with SARS-CoV-2 infection: dysregulation of the immune response across the age spectrum. *J Clin Invest* 2020; 130: 6194–6197.
10 Cattaneo P, Volpe A, Cardellino CS, *et al.* Multisystem inflammatory syndrome in an adult (MIS-A) successfully treated with anakinra and glucocorticoids. *Microorganisms* 2021; 9: 1393.
11 Guzik TJ, Mohiddin SA, Dimarco A, *et al.* COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res* 2020; 116: 1666–1687.
12 Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol* 2020; 5: 562–569.

13 Hoffmann M, Kleine-Weber H, Schroeder S, *et al.* SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; 181: 271–280.e278.
14 Hoffmann M, Kleine-Weber H, Pöhlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. *Mol Cell* 2020; 78: 779–784.e775.
15 Coutard B, Valle C, de Lamballerie X, *et al.* The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral Res* 2020; 176: 104742.
16 Xia S, Lan Q, Su S, *et al.* The role of furin cleavage site in SARS-CoV-2 spike protein-mediated membrane fusion in the presence or absence of trypsin. *Signal Transduct Target Ther* 2020; 5: 92.
17 Inde Z, Croker BA, Yapp C, *et al.* Age-dependent regulation of SARS-CoV-2 cell entry genes and cell death programs correlates with COVID-19 severity. *Sci Adv* 2021; 7: eabf8609.
18 Li MY, Li L, Zhang Y, *et al.* Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty* 2020; 9: 45.
19 McCoy K, Peterson A, Tian Y, *et al.* Immunogenetic association underlying severe COVID-19. *Vaccines* 2020; 8: 700.
20 Pairo-Castineira E, Clohisey S, Klaric L, *et al.* Genetic mechanisms of critical illness in COVID-19. *Nature* 2021; 591: 92–98.
21 Ellinghaus D, Degenhardt F, Bujanda L, *et al.* Genomewide association study of severe COVID-19 with respiratory failure. *N Engl J Med* 2020; 383: 1522–1534.
22 COVID-19 Host Genetics Initiative. Mapping the human genetic architecture of COVID-19. *Nature* 2021; 600: 472–477.
23 Tay MZ, Poh CM, Rénia L, *et al.* The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; 20: 363–374.
24 Kaneko N, Kuo HH, Boucau J, *et al.* Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19. *Cell* 2020; 183: 143–157.e113.
25 Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. *Clin Immunol* 2020; 215: 108427.
26 Hadjadj J, Yatim N, Barnabei L, *et al.* Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 2020; 369: 718–724.
27 Arunachalam PS, Wimmers F, Mok CKP, *et al.* Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans. *Science* 2020; 369: 1210–1220.
28 Lopez L, Sang PC, Tian Y, *et al.* Dysregulated interferon response underlying severe COVID-19. *Viruses* 2020; 12: 1433.
29 McNab F, Mayer-Barber K, Sher A, *et al.* Type I interferons in infectious disease. *Nat Rev Immunol* 2015; 15: 87–103.
30 Channappanavar R, Fehr AR, Zheng J, *et al.* IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. *J Clin Invest* 2019; 129: 3625–3639.
31 King C, Sprent J. Dual nature of type I interferons in SARS-CoV-2-induced inflammation. *Trends Immunol* 2021; 42: 312–322.
32 Channappanavar R, Fehr AR, Vijay R, *et al.* Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. *Cell Host Microbe* 2016; 19: 181–193.
33 Lucas C, Wong P, Klein J, *et al.* Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 2020; 584: 463–469.
34 Blanco-Melo D, Nilsson-Payant BE, Liu WC, *et al.* Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell* 2020; 181: 1036–1045.e1039.
35 Rodríguez Y, Novelli L, Rojas M, *et al.* Autoinflammatory and autoimmune conditions at the crossroad of COVID-19. *J Autoimmun* 2020; 114: 102506.
36 Guarnera A, Podda P, Santini E, *et al.* Differential diagnoses of COVID-19 pneumonia: the current challenge for the radiologist–a pictorial essay. *Insights Imaging* 2021; 12: 34.
37 Hani C, Trieu NH, Saab I, *et al.* COVID-19 pneumonia: a review of typical CT findings and differential diagnosis. *Diagn Interv Imaging* 2020; 101: 263–268.
38 Bhatnagar J, Gary J, Reagan-Steiner S, *et al.* Evidence of severe acute respiratory syndrome coronavirus 2 replication and tropism in the lungs, airways, and vascular endothelium of patients with fatal coronavirus disease 2019: an autopsy case series. *J Infect Dis* 2021; 223: 752–764.
39 Hönzke K, Obermayer B, Mache C, *et al.* Human lungs show limited permissiveness for SARS-CoV-2 due to scarce ACE2 levels but virus-induced expansion of inflammatory macrophages. *Eur Respir J* 2022; 60: 2102725.
40 Dockrell DH, Russell CD, McHugh B, *et al.* Does autonomous macrophage-driven inflammation promote alveolar damage in COVID-19? *Eur Respir J* 2022; 60: 2201521.
41 Matheson NJ, Lehner PJ. How does SARS-CoV-2 cause COVID-19? *Science* 2020; 369: 510–511.
42 Kadkhoda K. COVID-19: an immunopathological view. *mSphere* 2020; 5: e00344-20.
43 Harapan H, Itoh N, Yufika A, *et al.* Coronavirus disease 2019 (COVID-19): a literature review. *J Infect Public Health* 2020; 13: 667–673.

44 Azkur AK, Akdis M, Azkur D, *et al.* Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy* 2020; 75: 1564–1581.
45 Ilias I, Zabuliene L. Hyperglycemia and the novel COVID-19 infection: possible pathophysiologic mechanisms. *Med Hypotheses* 2020; 139: 109699.
46 Liang Y, Wang ML, Chien CS, *et al.* Highlight of immune pathogenic response and hematopathologic effect in SARS-CoV, MERS-CoV, and SARS-Cov-2 infection. *Front Immunol* 2020; 11: 1022.
47 Zhou F, Yu T, Du R, *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: 1054–1062.
48 Levin M. Childhood multisystem inflammatory syndrome – a new challenge in the pandemic. *N Engl J Med* 2020; 383: 393–395.
49 Chiotos K, Bassiri H, Behrens EM, *et al.* Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. *J Pediatric Infect Dis Soc* 2020; 9: 393–398.
50 Cabrero-Hernández M, García-Salido A, Leoz-Gordillo I, *et al.* Severe SARS-CoV-2 infection in children with suspected acute abdomen: a case series from a tertiary hospital in Spain. *Pediatr Infect Dis J* 2020; 39: e195–e198.
51 Vieira CB, Ferreira AT, Cardoso FB, *et al.* Kawasaki-like syndrome as an emerging complication of SARS-CoV-2 infection in young adults. *Eur J Case Rep Intern Med* 2020; 7: 001886.
52 Morris SB, Schwartz NG, Patel P, *et al.* Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection – United Kingdom and United States, March–August 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 1450–1456.
53 Zheng Y, Zhuang MW, Han L, *et al.* Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) membrane (M) protein inhibits type I and III interferon production by targeting RIG-I/MDA-5 signaling. *Signal Transduct Target Ther* 2020; 5: 299.
54 Xia H, Cao Z, Xie X, *et al.* Evasion of type I interferon by SARS-CoV-2. *Cell Rep* 2020; 33: 108234.
55 Schroeder S, Pott F, Niemeyer D, *et al.* Interferon antagonism by SARS-CoV-2: a functional study using reverse genetics. *Lancet Microbe* 2021; 2: e210–e218.
56 Killingley B, Mann AJ, Kalinova M, *et al.* Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults. *Nat Med* 2022; 28: 1031–1041.
57 Oran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 infection: a narrative review. *Ann Intern Med* 2020; 173: 362–367.
58 Long QX, Tang XJ, Shi QL, *et al.* Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 2020; 26: 1200–1204.
59 Lei Q, Li Y, Hou HY, *et al.* Antibody dynamics to SARS-CoV-2 in asymptomatic COVID-19 infections. *Allergy* 2021; 76: 551–561.
60 Sekine T, Perez-Potti A, Rivera-Ballesteros O, *et al.* Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. *Cell* 2020; 183: 158–168.e114.
61 Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020; 324: 603–605.
62 Davis HE, Assaf GS, McCorkell L, *et al.* Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine* 2021; 38: 101019.
63 Townsend L, Dyer AH, Jones K, *et al.* Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS ONE* 2020; 15: e0240784.
64 Buonsenso D, Munblit D, De Rose C, *et al.* Preliminary evidence on long COVID in children. *Acta Paediatr* 2021; 110: 2208–2211.
65 Pretorius E, Vlok M, Venter C, *et al.* Persistent clotting protein pathology in long COVID/post-acute sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. *Cardiovasc Diabetol* 2021; 20: 172.
66 Oronsky B, Larson C, Hammond TC, *et al.* A review of persistent post-COVID syndrome (PPCS). *Clin Rev Allergy Immunol* 2023; 64: 66–74.
67 Satterfield BA, Bhatt DL, Gersh BJ. Cardiac involvement in the long-term implications of COVID-19. *Nat Rev Cardiol* 2022; 19: 332–341.
68 Debnath M, Banerjee M, Berk M. Genetic gateways to COVID-19 infection: implications for risk, severity, and outcomes. *FASEB J* 2020; 34: 8787–8795.
69 Meftahi GH, Jangravi Z, Sahraei H, *et al.* The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of 'inflame-aging'. *Inflamm Res* 2020; 69: 825–839.
70 Saheb Sharif-Askari N, Saheb Sharif-Askari F, Alabed M, *et al.* Airways expression of SARS-CoV-2 receptor, ACE2, and TMPRSS2 is lower in children than adults and increases with smoking and COPD. *Mol Ther Methods Clin Dev* 2020; 18: 1–6.
71 Kollmann TR, Levy O, Montgomery RR, *et al.* Innate immune function by Toll-like receptors: distinct responses in newborns and the elderly. *Immunity* 2012; 37: 771–783.
72 Dong X, Cao YY, Lu XX, *et al.* Eleven faces of coronavirus disease 2019. *Allergy* 2020; 75: 1699–1709.
73 Nguyen LH, Drew DA, Graham MS, *et al.* Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. *Lancet Public Health* 2020; 5: e475–e483.

74 Pinto BGG, Oliveira AER, Singh Y, *et al.* ACE2 expression is increased in the lungs of patients with comorbidities associated with severe COVID-19. *J Infect Dis* 2020; 222: 556–563.
75 Collin J, Byström E, Carnahan A, *et al.* Public health agency of Sweden's brief report: pregnant and postpartum women with severe acute respiratory syndrome coronavirus 2 infection in intensive care in Sweden. *Acta Obstet Gynecol Scand* 2020; 99: 819–822.
76 Li J, Wang X, Chen J, *et al.* Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. *Br J Haematol* 2020; 190: 24–27.
77 Wu Y, Feng Z, Li P, *et al.* Relationship between ABO blood group distribution and clinical characteristics in patients with COVID-19. *Clin Chim Acta* 2020; 509: 220–223.
78 Trouillet-Assant S, Viel S, Gaymard A, *et al.* Type I IFN immunoprofiling in COVID-19 patients. *J Allergy Clin Immunol* 2020; 146: 206–208.e202.
79 Knoll R, Schultze JL, Schulte-Schrepping J. Monocytes and macrophages in COVID-19. *Front Immunol* 2021; 12: 720109.
80 Kumagai Y, Takeuchi O, Kato H, *et al.* Alveolar macrophages are the primary interferon-α producer in pulmonary infection with RNA viruses. *Immunity* 2007; 27: 240–252.
81 Galati D, Zanotta S, Capitelli L, *et al.* A bird's eye view on the role of dendritic cells in SARS-CoV-2 infection: perspectives for immune-based vaccines. *Allergy* 2021; 77: 100–110.
82 Grant RA, Morales-Nebreda L, Markov NS, *et al.* Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. *Nature* 2021; 590: 635–641.
83 Lv J, Wang Z, Qu Y, *et al.* Distinct uptake, amplification, and release of SARS-CoV-2 by M1 and M2 alveolar macrophages. *Cell Discov* 2021; 7: 24.
84 Martines RB, Ritter JM, Matkovic E, *et al.* Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States. *Emerg Infect Dis* 2020; 26: 2005–2015.
85 Junqueira C, Crespo Â, Ranjbar S, *et al.* FcγR-mediated SARS-CoV-2 infection of monocytes activates inflammation. *Nature* 2022; 606: 576–584.
86 Boumaza A, Gay L, Mezouar S, *et al.* Monocytes and macrophages, targets of severe acute respiratory syndrome coronavirus 2: the clue for coronavirus disease 2019 immunoparalysis. *J Infect Dis* 2021; 224: 395–406.
87 Sefik E, Israelow B, Mirza H, *et al.* A humanized mouse model of chronic COVID-19. *Nat Biotechnol* 2022; 40: 906–920.
88 Dorward DA, Russell CD, Um IH, *et al.* Tissue-specific immunopathology in fatal COVID-19. *Am J Respir Crit Care Med* 2021; 203: 192–201.
89 Kim YM, Shin EC. Type I and III interferon responses in SARS-CoV-2 infection. *Exp Mol Med* 2021; 53: 750–760.
90 Cheung CY, Poon LL, Ng IH, *et al.* Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages in vitro: possible relevance to pathogenesis. *J Virol* 2005; 79: 7819–7826.
91 Onodi F, Bonnet-Madin L, Meertens L, *et al.* SARS-CoV-2 induces human plasmacytoid predendritic cell diversification *via* UNC93B and IRAK4. *J Exp Med* 2021; 218: e20201387.
92 Zhang Q, Bastard P, Liu Z, *et al.* Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 2020; 370: eabd4570.
93 Asano T, Boisson B, Onodi F, *et al.* X-linked recessive TLR7 deficiency in ∼1% of men under 60 years old with life-threatening COVID-19. *Sci Immunol* 2021; 6; eabl4348.
94 Bastard P, Gervais A, Le Voyer T, *et al.* Autoantibodies neutralizing type I IFNs are present in ∼4% of uninfected individuals over 70 years old and account for ∼20% of COVID-19 deaths. *Sci Immunol* 2021; 6: eabl4340.
95 Bastard P, Rosen LB, Zhang Q, *et al.* Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020; 370: eabd4585.
96 McGonagle D, O'Donnell JS, Sharif K, *et al.* Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol* 2020; 2: e437–e445.
97 Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 2020; 20: 355–362.
98 Rapkiewicz AV, Mai X, Carsons SE, *et al.* Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: a case series. *EClinicalMedicine* 2020; 24: 100434.
99 Bussani R, Schneider E, Zentilin L, *et al.* Persistence of viral RNA, pneumocyte syncytia and thrombosis are hallmarks of advanced COVID-19 pathology. *EBioMedicine* 2020; 61: 103104.
100 Klok FA, Kruip M, van der Meer NJM, *et al.* Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020; 191: 145–147.
101 Nicolai L, Leunig A, Brambs S, *et al.* Immunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy. *Circulation* 2020; 142: 1176–1189.
102 Loo J, Spittle DA, Newnham M. COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. *Thorax* 2021; 76: 412–420.

103 Ackermann M, Anders HJ, Bilyy R, *et al.* Patients with COVID-19: in the dark-NETs of neutrophils. *Cell Death Differ* 2021; 28: 3125–3139.

104 Middleton EA, He XY, Denorme F, *et al.* Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. *Blood* 2020; 136: 1169–1179.

105 Leppkes M, Knopf J, Naschberger E, *et al.* Vascular occlusion by neutrophil extracellular traps in COVID-19. *EBioMedicine* 2020; 58: 102925.

106 Veras FP, Pontelli MC, Silva CM, *et al.* SARS-CoV-2-triggered neutrophil extracellular traps mediate COVID-19 pathology. *J Exp Med* 2020; 217: e20201129.

107 Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation. *Nat Rev Immunol* 2007; 7: 803–815.

108 Zuo Y, Estes SK, Ali RA, *et al.* Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. *Sci Transl Med* 2020; 12: eabd3876.

109 Goldman M, Hermans C. Thrombotic thrombocytopenia associated with COVID-19 infection or vaccination: possible paths to platelet factor 4 autoimmunity. *PLoS Med* 2021; 18: e1003648.

110 Yang X, Yang Q, Wang Y, *et al.* Thrombocytopenia and its association with mortality in patients with COVID-19. *J Thromb Haemost* 2020; 18: 1469–1472.

111 Wang EY, Mao T, Klein J, *et al.* Diverse functional autoantibodies in patients with COVID-19. *Nature* 2021; 595: 283–288.

112 Nazy I, Jevtic SD, Moore JC, *et al.* Platelet-activating immune complexes identified in critically ill COVID-19 patients suspected of heparin-induced thrombocytopenia. *J Thromb Haemost* 2021; 19: 1342–1347.

113 Perricone C, Agmon-Levin N, Ceccarelli F, *et al.* Genetics and autoantibodies. *Immunol Res* 2013; 56: 206–219.

114 Woodruff MC, Ramonell RP, Nguyen DC, *et al.* Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19. *Nat Immunol* 2020: 21: 1506–1516.

115 Yu K, He J, Wu Y, *et al.* Dysregulated adaptive immune response contributes to severe COVID-19. *Cell Res* 2020; 30: 814–816.

116 Negro F. Is antibody-dependent enhancement playing a role in COVID-19 pathogenesis? *Swiss Med Wkly* 2020; 150: w20249.

117 Cardozo T, Veazey R. Informed consent disclosure to vaccine trial subjects of risk of COVID-19 vaccines worsening clinical disease. *Int J Clin Pract* 2021; 75: e13795.

118 van Eeden C, Khan L, Osman MS, *et al.* Natural killer cell dysfunction and its role in COVID-19. *Int J Mol Sci* 2020; 21: 6351.

119 Poland GA, Ovsyannikova IG, Kennedy RB. SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates. *Lancet* 2020; 396: 1595–1606.

120 McMahan K, Yu J, Mercado NB, *et al.* Correlates of protection against SARS-CoV-2 in rhesus macaques. *Nature* 2021; 590: 630–634.

121 Buckland MS, Galloway JB, Fhogartaigh CN, *et al.* Treatment of COVID-19 with remdesivir in the absence of humoral immunity: a case report. *Nat Commun* 2020; 11: 6385.

122 Bange EM, Han NA, Wileyto P, *et al.* $CD8^+$ T cells contribute to survival in patients with COVID-19 and hematologic cancer. *Nat Med* 2021; 27: 1280–1289.

123 Zheng M, Gao Y, Wang G, *et al.* Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol* 2020; 17: 533–535.

124 Osman M, Faridi RM, Sligl W, *et al.* Impaired natural killer cell counts and cytolytic activity in patients with severe COVID-19. *Blood Adv* 2020; 4: 5035–5039.

125 Antonioli L, Fornai M, Pellegrini C, *et al.* NKG2A and COVID-19: another brick in the wall. *Cell Mol Immunol* 2020; 17: 672–674.

126 Cifaldi L, Prencipe G, Caiello I, *et al.* Inhibition of natural killer cell cytotoxicity by interleukin-6: implications for the pathogenesis of macrophage activation syndrome. *Arthritis Rheumatol* 2015; 67: 3037–3046.

127 Wu J, Gao FX, Wang C, *et al.* IL-6 and IL-8 secreted by tumour cells impair the function of NK cells *via* the STAT3 pathway in oesophageal squamous cell carcinoma. *J Exp Clin Cancer Res* 2019; 38: 321.

128 Cho JH, Kim HO, Webster K, *et al.* Calcineurin-dependent negative regulation of CD94/NKG2A expression on naive $CD8^+$ T cells. *Blood* 2011; 118: 116–128.

129 Bortolotti D, Gentili V, Rizzo S, *et al.* SARS-CoV-2 spike 1 protein controls natural killer cell activation *via* the HLA-E/NKG2A pathway. *Cells* 2020; 9: 1975.

130 Knuschke T, Rotan O, Bayer W, *et al.* Induction of type I interferons by therapeutic nanoparticle-based vaccination is indispensable to reinforce cytotoxic $CD8^+$ T cell responses during chronic retroviral infection. *Front Immunol* 2018; 9: 614.

131 Madera S, Rapp M, Firth MA, *et al.* Type I IFN promotes NK cell expansion during viral infection by protecting NK cells against fratricide. *J Exp Med* 2016; 213: 225–233.

132 Tovey MG, Lallemand C, Thyphronitis G. Adjuvant activity of type I interferons. *Biol Chem* 2008; 389: 541–545.

133 Neufeldt CJ, Cerikan B, Cortese M, *et al.* SARS-CoV-2 infection induces a pro-inflammatory cytokine response through cGAS-STING and NF-κB. *Commun Biol* 2022; 5: 45.

134 Berthelot JM, Drouet L, Lioté F. Kawasaki-like diseases and thrombotic coagulopathy in COVID-19: delayed over-activation of the STING pathway? *Emerg Microbes Infect* 2020; 9: 1514–1522.

135 Lee JS, Park S, Jeong HW, *et al.* Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19. *Sci Immunol* 2020; 5: eabd1554.

136 Berthelot JM, Lioté F. COVID-19 as a STING disorder with delayed over-secretion of interferon-beta. *EBioMedicine* 2020; 56: 102801.

137 Su CM, Wang L, Yoo D. Activation of NF-κB and induction of proinflammatory cytokine expressions mediated by ORF7a protein of SARS-CoV-2. *Sci Rep* 2021; 11: 13464.

138 Del Valle DM, Kim-Schulze S, Huang HH, *et al.* An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020; 26: 1636–1643.

139 Abers MS, Delmonte OM, Ricotta EE, *et al.* An immune-based biomarker signature is associated with mortality in COVID-19 patients. *JCI Insight* 2021; 6: e144455.

140 Maeda K, Malykhin A, Teague-Weber BN, *et al.* Interleukin-6 aborts lymphopoiesis and elevates production of myeloid cells in systemic lupus erythematosus-prone B6.Sle1.Yaa animals. *Blood* 2009; 113: 4534–4540.

141 Schulte-Schrepping J, Reusch N, Paclik D, *et al.* Severe COVID-19 is marked by a dysregulated myeloid cell compartment. *Cell* 2020; 182: 1419–1440.e1423.

142 Giamarellos-Bourboulis EJ, Netea MG, Rovina N, *et al.* Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe* 2020; 27: 992–1000.e1003.

143 Prieto-Pérez L, Fortes J, Soto C, *et al.* Histiocytic hyperplasia with hemophagocytosis and acute alveolar damage in COVID-19 infection. *Mod Pathol* 2020; 33: 2139–2146.

144 Silvin A, Chapuis N, Dunsmore G, *et al.* Elevated calprotectin and abnormal myeloid cell subsets discriminate severe from mild COVID-19. *Cell* 2020; 182: 1401–1418.e1418.

145 Liao M, Liu Y, Yuan J, *et al.* Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat Med* 2020; 26: 842–844.

146 Chernyak BV, Popova EN, Prikhodko AS, *et al.* COVID-19 and oxidative stress. *Biochemistry* 2020; 85: 1543–1553.

147 Felsenstein S, Herbert JA, McNamara PS, *et al.* COVID-19: immunology and treatment options. *Clin Immunol* 2020; 215: 108448.

148 Reyes L, M AS-G, Morrison T, *et al.* A type I IFN, prothrombotic hyperinflammatory neutrophil signature is distinct for COVID-19 ARDS. *Wellcome Open Res* 2021; 6: 38.

149 Savla SR, Prabhavalkar KS, Bhatt LK. Cytokine storm associated coagulation complications in COVID-19 patients: pathogenesis and management. *Expert Rev Anti Infect Ther* 2021; 19: 1397–1413.

150 Peddapalli A, Gehani M, Kalle AM, *et al.* Demystifying excess immune response in COVID-19 to reposition an orphan drug for down-regulation of NF-κB: a systematic review. *Viruses* 2021; 13: 378.

151 Carter MJ, Fish M, Jennings A, *et al.* Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. *Nat Med* 2020; 26: 1701–1707.

152 Consiglio CR, Cotugno N, Sardh F, *et al.* The immunology of multisystem inflammatory syndrome in children with COVID-19. *Cell* 2020; 183: 968–981.e967.

153 Anderson EM, Diorio C, Goodwin EC, *et al.* Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) antibody responses in children with multisystem inflammatory syndrome in children (MIS-C) and mild and severe coronavirus disease 2019 (COVID-19). *J Pediatric Infect Dis Soc* 2021; 10: 669–673.

154 Rostad CA, Chahroudi A, Mantus G, *et al.* Quantitative SARS-CoV-2 serology in children with multisystem inflammatory syndrome (MIS-C). *Pediatrics* 2020; 146: e2020018242.

155 Beckmann ND, Comella PH, Cheng E, *et al.* Downregulation of exhausted cytotoxic T cells in gene expression networks of multisystem inflammatory syndrome in children. *Nat Commun* 2021; 12: 4854.

156 Gruber CN, Patel RS, Trachtman R, *et al.* Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). *Cell* 2020; 183: 982–995.e914.

157 Weisberg SP, Connors TJ, Zhu Y, *et al.* Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. *Nat Immunol* 2021; 22: 25–31.

158 Nakra NA, Blumberg DA, Herrera-Guerra A, *et al.* Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. *Children* 2020; 7: 69.

159 Jiang L, Tang K, Levin M, *et al.* COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis* 2020; 20: e276–e288.

160 Bukulmez H. Current understanding of multisystem inflammatory syndrome (MIS-C) following COVID-19 and its distinction from Kawasaki disease. *Curr Rheumatol Rep* 2021; 23: 58.

161 Wu Y, Kang L, Guo Z, *et al.* Incubation period of COVID-19 caused by unique SARS-CoV-2 strains: a systematic review and meta-analysis. *JAMA Netw Open* 2022; 5: e2228008.

162 Cascella M, Rajnik M, Aleem A, *et al.* Features, Evaluation, and Treatment of Coronavirus (COVID-19). Treasure Island, FL, StatPearls Publishing LLC., 2022.

163 Infectious Diseases Society of America. Multisystem inflammatory syndrome in adults (MIS-A). www.idsociety.org/covid-19-real-time-learning-network/disease-manifestations--complications/multisystem-inflammatory-syndrome-in-adults-mis-a/ Date last updated: 24 June 2022.

164 Vella LA, Giles JR, Baxter AE, *et al.* Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19. *Sci Immunol* 2021; 6: eabf7570.

165 Li Y, Zhou W, Yang L, *et al.* Physiological and pathological regulation of ACE2, the SARS-CoV-2 receptor. *Pharmacol Res* 2020; 157: 104833.

166 Cristiani L, Mancino E, Matera L, *et al.* Will children reveal their secret? The coronavirus dilemma. *Eur Respir J* 2020; 55: 2000749.

167 Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nat Rev Immunol* 2020; 20: 453–454.

168 Schaefer IM, Padera RF, Solomon IH, *et al. In situ* detection of SARS-CoV-2 in lungs and airways of patients with COVID-19. *Mod Pathol* 2020; 33: 2104–2114.

169 Dhar D, Dey T, Samim MM, *et al.* Systemic inflammatory syndrome in COVID-19-SISCoV study: systematic review and meta-analysis. *Pediatr Res* 2021; 91: 1334–1349.

170 Tenforde MW, Morris SB. Multisystem inflammatory syndrome in adults: coming into focus. *Chest* 2021; 159: 471–472.

171 Majoros A, Platanitis E, Kernbauer-Hölzl E, *et al.* Canonical and non-canonical aspects of JAK-STAT signaling: lessons from interferons for cytokine responses. *Front Immunol* 2017; 8: 29.

172 Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. *Nat Rev Immunol* 2014; 14: 36–49.

173 de Cevins C, Luka M, Smith N, *et al.* A monocyte/dendritic cell molecular signature of SARS-CoV-2-related multisystem inflammatory syndrome in children with severe myocarditis. *Med* 2021; 2: 1072–1092.

174 Porritt RA, Binek A, Paschold L, *et al.* The autoimmune signature of hyperinflammatory multisystem inflammatory syndrome in children. *J Clin Invest* 2021; 131: e151520.

175 Cheng MH, Zhang S, Porritt RA, *et al.* Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation. *Proc Natl Acad Sci USA* 2020; 117: 25254–25262.

176 Moreews M, Le Gouge K, Khaldi-Plassart S, *et al.* Polyclonal expansion of TCR Vbeta 21.3^{+} CD4^{+} and CD8^{+} T cells is a hallmark of multisystem inflammatory syndrome in children. *Sci Immunol* 2021; 6: eabh1516.

177 Kouo T, Chaisawangwong W. SARS-CoV-2 as a superantigen in multisystem inflammatory syndrome in children. *J Clin Invest* 2021; 131: e149327.

178 Martinez OM, Bridges ND, Goldmuntz E, *et al.* The immune roadmap for understanding multi-system inflammatory syndrome in children: opportunities and challenges. *Nat Med* 2020; 26: 1819–1824.

179 Faulkner L, Cooper A, Fantino C, *et al.* The mechanism of superantigen-mediated toxic shock: not a simple Th1 cytokine storm. *J Immunol* 2005; 175: 6870–6877.

180 Dolhnikoff M, Ferreira Ferranti J, de Almeida Monteiro RA, *et al.* SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome. *Lancet Child Adolesc Health* 2020; 4: 790–794.

181 Esposito S, Principi N. Multisystem inflammatory syndrome in children related to SARS-CoV-2. *Paediatr Drugs* 2021; 23: 119–129.

182 Sancho-Shimizu V, Brodin P, Cobat A, *et al.* SARS-CoV-2-related MIS-C: A key to the viral and genetic causes of Kawasaki disease? *J Exp Med* 2021; 218: e20210446.

183 Lee PY, Platt CD, Weeks S, *et al.* Immune dysregulation and multisystem inflammatory syndrome in children (MIS-C) in individuals with haploinsufficiency of SOCS1. *J Allergy Clin Immunol* 2020; 146: 1194–1200.e1191.

184 Chou J, Platt CD, Habiballah S, *et al.* Mechanisms underlying genetic susceptibility to multisystem inflammatory syndrome in children (MIS-C). *J Allergy Clin Immunol* 2021; 148: 732–738.

185 Ronit A, Jørgensen SE, Roed C, *et al.* Host genetics and antiviral immune responses in adult patients with multisystem inflammatory syndrome. *Front Immunol* 2021; 12: 718744.

186 Mudd JC, Panigrahi S, Kyi B, *et al.* Inflammatory function of CX3CR1^{+} CD8^{+} T cells in treated HIV infection is modulated by platelet interactions. *J Infect Dis* 2016; 214: 1808–1816.

187 Umehara H, Tanaka M, Sawaki T, *et al.* Fractalkine in rheumatoid arthritis and allied conditions. *Mod Rheumatol* 2006; 16: 124–130.

188 Fraser DD, Patterson EK, Daley M, *et al.* Case report: inflammation and endothelial injury profiling of COVID-19 pediatric multisystem inflammatory syndrome (MIS-C). *Front Pediatr* 2021; 9: 597926.

189 Islam T, Hasan M, Rahman MS, *et al.* Comparative evaluation of authorized drugs for treating COVID-19 patients. *Health Sci Rep* 2022; 5: e671.

190 Yasuda Y, Hirayama Y, Uemasu K, *et al.* Efficacy of the combination of baricitinib, remdesivir, and dexamethasone in hypoxic adults with COVID-19: a retrospective study. *Respir Med Res* 2022; 81: 100903.

191 Gupte V, Hegde R, Sawant S, *et al.* Safety and clinical outcomes of remdesivir in hospitalised COVID-19 patients: a retrospective analysis of active surveillance database. *BMC Infect Dis* 2022; 22: 1.

192 De Pascale G, Cutuli SL, Carelli S, *et al.* Remdesivir plus dexamethasone in COVID-19: a cohort study of severe patients requiring high flow oxygen therapy or non-invasive ventilation. *PLoS ONE* 2022; 17: e0267038.

193 Anastassopoulou C, Hatziantoniou S, Boufidou F, *et al.* The role of oral antivirals for COVID-19 treatment in shaping the pandemic landscape. *J Pers Med* 2022; 12: 439.

194 National Institutes of Health. COVID-19 treatment guidelines. www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/ Date last accessed: 26 January 2023.

195 NIDirect Government Services. Treatments for coronavirus (COVID-19). www.nidirect.gov.uk/articles/treatments-coronavirus-covid-19 Date last accessed: 26 January 2023

196 Bryushkova EA, Skatova VD, Mutovina ZY, *et al.* Tocilizumab, netakimab, and baricitinib in patients with mild-to-moderate COVID-19: An observational study. *PLoS ONE* 2022; 17: e0273340.

197 Xibille Friedmann DX, Carrillo Vazquez SM. POS1233 use of baricitinib and tocilizumab for the treatment of moderate to severe covid-19 in hospitalized patients. *Annal Rheum Dis* 2021; 80: Suppl. 1, 899–900.

198 National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: managing COVID-19. www.nice.org.uk/guidance/ng191/resources/fully-accessible-version-of-the-guideline-pdf-pdf-51035553326 Date last updated: 4 January 2023.

199 Ouldali N, Toubiana J, Antona D, *et al.* Association of intravenous immunoglobulins plus methylprednisolone *vs* immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. *JAMA* 2021; 325: 855–864.

200 Son MBF, Murray N, Friedman K, *et al.* Multisystem inflammatory syndrome in children - initial therapy and outcomes. *N Engl J Med* 2021; 385: 23–34.

201 Belhadjer Z, Auriau J, Méot M, *et al.* Addition of corticosteroids to immunoglobulins is associated with recovery of cardiac function in multi-inflammatory syndrome in children. *Circulation* 2020; 142: 2282–2284.

202 Feldstein LR, Rose EB, Horwitz SM, *et al.* Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med* 2020; 383: 334–346.

203 Kaushik A, Gupta S, Sood M, *et al.* A systematic review of multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. *Pediatr Infect Dis J* 2020; 39: e340–e346.

204 Goldenberg NA, Sochet A, Albisetti M, *et al.* Consensus-based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalized for COVID-19-related illness. *J Thromb Haemost* 2020; 18: 3099–3105.

205 Whitworth H, Sartain SE, Kumar R, *et al.* Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C. *Blood* 2021; 138: 190–198.