Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

process is dominant in a given patient at a given time. Corticosteroids can have a deleterious effect in the context of immunosuppression by promoting viral replication and prolonging viral infections.[12] In contrast, a recent study suggested that corticosteroids might be beneficial only in patients with severe COVID-19 and a hyperinflammatory response.[13] Likewise, a glaring absence in many conceptual immunobiological frameworks is the consistent and robust association of COVID-19 severity with older age. Although the reasons for this association remain incompletely understood, the immense protection from severe COVID-19 afforded by youth might imply that immunosenescence plays a crucial part in the host response, which is responsible for viral clearance in severe COVID-19.[14] Analysis of data that are able to distill these many competing factors at an individual level might be needed to fully realise the potential of immunotherapies in COVID-19.

Taken together, the first three papers in this Series[2,3,5] suggest that a precision-based approach to treatment might be needed, which is one of the central challenges facing the field. Phenotypes based on a systemic inflammatory response or an immunosuppressive state, or on biological markers of coagulopathy and endothelial dysfunction, might help to identify treatment-responsive subgroups of patients. COVID-19 phenotypes based on the temporal kinetics of immunological markers or disease trajectories are also of interest, and might be key to unlocking the optimum timing and type of immunomodulatory therapy. The role of different SARS-CoV-2 variants and the resulting host response also warrant further evaluation. Finally, studying host immune responses in the lungs will be important, although this comes with its own technical challenges. Future clinical practice is likely to involve targeted therapies based on biological, genetic, or functional immunophenotyping. Until such a time, researchers and clinicians must continue to carry out careful and well planned RCTs, acknowledge the complexity of the challenge we face, and assiduously collect biological specimens to better understand host immune responses to pathogens and their implications for the treatment of patients.

PS declares no competing interests. CSC has received grant funding from the US National Institutes of Health (HL140026), US Food and Drug Administration, Roche-Genentech, Quantum Leap Healthcare Collaborative, and Bayer Pharmaceuticals, and has served as a consultant to Vasomune, Quark, and Gen1e Life Sciences.

*Pratik Sinha, Carolyn S Calfee
p.sinha@wustl.edu

Division of Clinical and Translational Research and Division of Critical Care, Department of Anesthesiology, Washington University School of Medicine, St Louis, MO 63110, USA (PS); Department of Medicine, Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, and Cardiovascular Research Institute, University of California San Francisco, San Francisco, CA, USA (CSC)

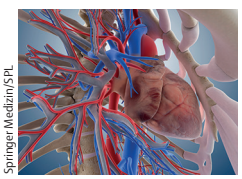
1 RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397:** 1637–45.
2 Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med* 2021; published online May 6. https://doi.org /10.1016/S2213-2600(21)00218-6.
3 McElvaney O, Curley G, Rose-John S, McElvaney NG. Interleukin-6: obstacles to targeting a complex cytokine in critical illness. *Lancet Respir Med* 2021; published online April 16. https://doi.org/10.1016/S2213-2600(21)00103-X.
4 The REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021; **384:** 1491–502.
5 Angriman F, Ferreyro BL, Burry L, et al. Interleukin-6 blockade in patients with COVID-19: placing clinical trials into context. *Lancet Respir Med* 2021; published online April 27. https://doi.org/10.1016/S2213-2600(21)00139-9.
6 Dodd LE, Freidlin B, Korn EL. Platform trials — beware the noncomparable control group. *N Engl J Med* 2021; **384:** 1572–73.
7 Normand ST. The RECOVERY platform. *N Engl J Med* 2021; **384:** 757–58.
8 Challen R, Brooks-Pollock E, Read JM, Dyson L, Tsaneva-Atanasova K, Danon L. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. *BMJ* 2021; **372:** n579.
9 Churpek MM, Gupta S, Spicer AB, et al. Hospital-level variation in death for critically ill patients with COVID-19. *Am J Respir Crit Care Med* 2021; published online April 23. https://doi.org/10.1164/rccm.202012-4547OC.
10 Combes AJ, Courau T, Kuhn NF, et al. Global absence and targeting of protective immune states in severe COVID-19. *Nature* 2021; **591:** 124–30.
11 Remy KE, Mazer M, Striker DA, et al. Severe immunosuppression and not a cytokine storm characterizes COVID-19 infections. *JCI Insight* 2020; **5:** e140329.
12 Hui DS. Systemic corticosteroid therapy may delay viral clearance in patients with Middle East respiratory syndrome coronavirus infection. *Am J Respir Crit Care Med* 2018; **197:** 700–01.
13 Chen H, Xie J, Su N, et al. Corticosteroid therapy is associated with improved outcome in critically ill patients with COVID-19 with hyperinflammatory phenotype. *Chest* 2021; **159:** 1793–802.
14 Bajaj V, Gadi N, Spihlman AP, Wu SC, Choi CH, Moulton VR. Aging, immunity, and COVID-19: how age influences the host immune response to coronavirus infections? *Front Physiol* 2020; **11:** 571416.

Vascular mechanisms and manifestations of COVID-19

Published **Online** May 17, 2021 https://doi.org/10.1016/S2213-2600(21)00221-6

See **Series** page 622, 643, 655 and 665

Severe COVID-19 is dominated by a multifaceted severe respiratory infection. The pathophysiology of acute disease is the focus of a Series of four papers in *The Lancet Respiratory Medicine*. Dennis McGonagle and colleagues[1] propose that COVID-19 simultaneously affects three compartments of the lungs, thereby leading to disruption of oxygenation: inflammation of the alveolar space, immunothrombosis of the juxtaposed pulmonary vascular compartment, and thrombotic obstruction of the pulmonary and bronchial circulation. Apart from the respiratory features of COVID-19, many extrapulmonary manifestations can occur as


Springer Medizin/SPL

well. Some of these disease characteristics might be expected in patients with severe acute lung injury and a systemic inflammatory response; however, COVID-19 includes some complications that seem to be specific to SARS-CoV-2 infection. Marcin Osuchowski and colleagues[2] describe the most common phenotypes of COVID-19 in their comprehensive review of disease pathophysiology.

A remarkable finding in patients with severe COVID-19 are coagulation abnormalities, which have been associated with respiratory deterioration and death. COVID-19-associated coagulopathy mimics other systemic coagulopathies that are regularly seen in severe infections, most notably disseminated intravascular coagulation (DIC). However, COVID-19 has clinical and laboratory features that are distinctly different from the typical presentation of DIC.[3] Elevated D-dimer concentrations—sometimes many times higher than the levels (<0·5 mg/L) seen in healthy individuals—can be found in more than 50% of patients with COVID-19 and are related to a poor outcome.[4] A mild thrombocytopenia can also occur, with a platelet count between 100×10^9 and 150×10^9 per L, but more severe thrombocytopenia is seen in less than 5% of patients with COVID-19. A meta-analysis[5] showed that the low platelet counts (about -30×10^9 per L, 95% CI -35×10^9 to -29×10^9) in critically ill patients with COVID-19 and thrombocytopenia—defined as counts below the lower limit of the reference range—were associated with a higher risk of severe disease. However, in contrast to low platelet counts seen in other severe infections, moderate thrombocytopenia in COVID-19 has not been associated with mortality.

Coagulation abnormalities in severe COVID-19 are associated with a high risk of thrombotic vascular complications, in particular venous thromboembolism.[6] Pulmonary thrombosis or embolism can contribute to a sudden deterioration of pulmonary oxygen exchange, which is occasionally seen in patients with COVID-19. Local formation of platelet clots, as a manifestation of thrombotic microangiopathy, might contribute to organ dysfunction. Clinical observational studies in almost 2000 patients found venous thromboembolism in up to 35% of those with severe COVID-19.[6] Several retrospective studies point to a higher risk of venous thromboembolism in patients with more severe COVID-19 coagulopathy. The relevance of microvascular thrombosis for organ dysfunction has also been suggested by post-mortem pathological studies. Several reports highlight vascular wall thickening, stenosis of the vascular lumen, and microthrombus formation associated with COVID-19-related acute respiratory distress syndrome (ARDS).[7] Similar pathological observations have been made in the vasculature of other organs.

In severe COVID-19, systemic levels of pro-inflammatory cytokines are markedly increased.[2] In a subset of the most severely affected patients, a so-called cytokine storm can be detected, characterised by high levels of proinflammatory cytokines and chemokines.[8] In particular, interleukin-6 (IL-6) has gained attention as one of the central mediators of the inflammatory response to COVID-19, as extensively reviewed by Oliver McElvaney and colleagues[9] in this Series. IL-6 is also relevant for the vascular complications seen in COVID-19, because this pleiotropic cytokine induces tissue factor expression on monocytes and macrophages, which consequently leads to thrombin generation.

Direct viral infection of endothelial cells, which abundantly express ACE2, can result in widespread endothelial dysfunction associated with recruitment of a vascular inflammatory response, which is presumably more exaggerated in patients with pre-existing vascular disease.[10] The simultaneous presence of vascular inflammation and coagulopathy might explain the high incidence of thromboembolic complications in patients with COVID-19.[6] Direct endothelial infection by SARS-CoV-2 might also explain the remarkable fibrinolytic profile of COVID-19, as the endothelium is the principal storage site of plasminogen activators. Experiments in mice with a targeted deletion of the urokinase-type plasminogen gene pointed to a urokinase-driven pathway as an important factor in mortality.[11] It is likely that inflammation-driven endothelial cell perturbation results in substantial release of plasminogen activators, which might explain the high levels of D-dimer in the most severely affected patients with COVID-19. Also, plasmin effects on metalloproteinases can result in extracellular matrix modification, expediting capillary leakage and lung oedema. Of note, the effects on plasminogen activators do not translate into a hyperfibrinolytic state or an increased risk of systemic bleeding in patients with COVID-19. Endothelial infection and ensuing endothelial cell injury can provide an excellent

scaffold for intravascular thrombus formation. It might also cause thrombotic microangiopathy in the microvasculature due to increased platelet–vessel wall interaction, as a consequence of the release of high-molecular-weight multimers of von Willebrand factor that are insufficiently cleaved by deficient ADAMTS13.

A marked relationship exists between broncho-alveolar coagulation and fibrinolysis, and the development of ARDS, in which intrapulmonary fibrin deposition as a result of deranged bronchoalveolar fibrin turnover is a crucial step. The clinical and laboratory picture of ARDS in ventilated patients with COVID-19 and important coagulation abnormalities suggests a potential role for bronchoalveolar fibrin turnover in the most severe disease.

As local and systemic immunothrombosis seem to have a central role in pulmonary and extrapulmonary vascular complications in COVID-19, therapeutic intervention in this process seems rational.[12] Besides general anti-inflammatory strategies (eg, dexamethasone), anti-IL-6 approaches have proved to be effective, as reviewed in this Series by Federico Angriman and colleagues.[8] Antithrombotic prophylaxis is another approach that might be beneficial. In a retrospective study of 449 patients who were admitted to hospital with severe COVID-19, mortality was lower in those who received prophylactic heparin than in patients who did not receive anticoagulant treatment;[13] among participants with more extensive coagulopathy, mortality was lower in heparin-treated patients. In fact, ample evidence exists to support the use of prophylactic low-molecular-weight heparin for the prevention of venous thromboembolism in all critically ill patients. Although the hypercoagulable state and the increased risk of thrombosis in patients with severe COVID-19 suggest that higher doses of heparin might be beneficial, this was not shown in a large randomised controlled trial,[14] and higher doses of heparin were associated with more haemorrhagic complications. Ongoing large, randomised studies—eg, REMAP-CAP (EudraCT 2015-002340-14) and RECOVERY (2020-001113-21)—are investigating the addition of antiplatelet agents to the antithrombotic regime.

We declare no competing interests.

Marcel Levi, Michiel Coppens
m.m.levi@amsterdamumc.nl

Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam, Netherlands (ML); University College London Hospitals NHS Foundation Trust, Department of Medicine, and Cardiometabolic Programme—National Institute for Health Research UCLH/UCL Biomedical Research Centre, London, UK (ML, MC)

1 McGonagle D, Bridgewood C, Meaney J. A tricompartmental model of lung oxygenation disruption to explain pulmonary and systemic pathology in severe COVID-19. *Lancet Respir Med* 2021; published online May 17. https://doi.org/S2213-2600(21)00213-7.
2 Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. *Lancet Respir Med* 2021; published online May 6. https://doi.org/S2213-2600(21)00218-6.
3 Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol* 2020; **7:** e438–40.
4 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:** 1054–62.
5 Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta* 2020; **506:** 145–48.
6 Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and venous thromboembolism: a meta-analysis of literature studies. *Semin Thromb Hemost* 2020; **46:** 763–71.
7 Damiani S, Fiorentino M, De Palma A, et al. Pathological post-mortem findings in lungs infected with SARS-CoV-2. *J Pathol* 2021; **253:** 31–40.
8 Angriman F, Ferreyro BL, Burry L, et al. Interleukin-6 blockade in patients with COVID-19: placing clinical trials into context. *Lancet Respir Med* 2021; published online April 27. https://doi.org/10.1016/S2213-2600(21)00139-9.
9 McElvaney O, Curley G, Rose-John S, McElvaney NG. Interleukin-6: obstacles to targeting a complex cytokine in critical illness. *Lancet Respir Med* 2021; published online April 16. https://doi.org/10.1016/S2213-2600(21)00103-X.
10 Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395:** 1417–18.
11 Gralinski LE, Bankhead A, Jeng S, et al. Mechanisms of severe acute respiratory syndrome coronavirus-induced acute lung injury. *mBio* 2013; **4:** e00271-13.
12 Bonaventura A, Vecchié A, Dagna L, et al. Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. *Nat Rev Immunol* 2021: **21:** 319–29.
13 Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020; **18:** 1094–99.
14 INSPIRATION Investigators. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit. *JAMA* 2021; **325:** 1620–30.

Non-invasive respiratory support strategies in COVID-19

Published **Online**
April 16, 2021
https://doi.org/10.1016/S2213-2600(21)00168-5

In hospitalised patients with COVID-19, an increase in oxygen requirements prompts the clinician to decide how and when to escalate treatment. A key treatment goal is to avoid, where possible, the need for invasive mechanical ventilation. However, up to 20% of hospitalised patients in the UK require admission to critical care units, and around 40% of those requiring invasive mechanical ventilation for