

COVID-19: consider cytokine storm syndromes and immunosuppression

As of March 12, 2020, coronavirus disease 2019 (COVID-19) has been confirmed in 125 048 people worldwide, carrying a mortality of approximately 3·7%,¹ compared with a mortality rate of less than 1% from influenza. There is an urgent need for effective treatment. Current focus has been on the development of novel therapeutics, including antivirals and vaccines. Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome. We recommend identification and treatment of hyperinflammation using existing, approved therapies with proven safety profiles to address the immediate need to reduce the rising mortality.

Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality.² Secondary haemophagocytic lymphohistiocytosis (sHLH) is an under-recognised, hyperinflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia with multiorgan failure. In adults, sHLH is most commonly triggered by viral infections³ and occurs in 3·7–4·3% of sepsis cases.⁴ Cardinal features of sHLH include unremitting fever, cytopenias, and hyperferritinaemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients.⁵ A cytokine profile resembling sHLH is associated with COVID-19 disease severity, characterised by increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon- γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- α , and tumour necrosis factor- α .⁶ Predictors of fatality from a recent retrospective, multicentre study of 150 confirmed COVID-19 cases

in Wuhan, China, included elevated ferritin (mean 1297·6 ng/ml in non-survivors vs 614·0 ng/ml in survivors; $p < 0\cdot001$) and IL-6 ($p < 0\cdot0001$),² suggesting that mortality might be due to virally driven hyperinflammation.

As during previous pandemics (severe acute respiratory syndrome and Middle East respiratory syndrome), corticosteroids are not routinely recommended and might exacerbate COVID-19-associated lung injury.⁷

However, in hyperinflammation, immunosuppression is likely to be beneficial. Re-analysis of data from a phase 3 randomised controlled trial of IL-1 blockade (anakinra) in sepsis, showed significant survival benefit in patients with hyperinflammation, without increased adverse events.⁸ A multicentre, randomised controlled trial of tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), has been approved in patients with



Published Online
March 13, 2020
[https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0)

	Number of points
Temperature	
<38·4°C	0
38·4–39·4°C	33
>39·4°C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias*	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
<1·5 mmol/L	0
1·5–4·0 mmol/L	44
>4·0 mmol/L	64
Fibrinogen (g/L)	
>2·5 g/L	0
≤2·5 g/L	30
Ferritin ng/ml	
<2000 ng/ml	0
2000–6000 ng/ml	35
>6000 ng/ml	50
Serum aspartate aminotransferase	
<30 IU/L	0
≥30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression†	
No	0
Yes	18

The HScore¹¹ generates a probability for the presence of secondary HLH. HScores greater than 169 are 93% sensitive and 86% specific for HLH. Note that bone marrow haemophagocytosis is not mandatory for a diagnosis of HLH. HScores can be calculated using an online HScore calculator.¹¹ HLH=haemophagocytic lymphohistiocytosis. *Defined as either haemoglobin concentration of 9·2 g/dL or less (≤5·71 mmol/L), a white blood cell count of 5000 white blood cells per mm³ or less, or platelet count of 110 000 platelets per mm³ or less, or all of these criteria combined. †HIV positive or receiving long-term immunosuppressive therapy (ie, glucocorticoids, cyclosporine, azathioprine).

Table: HScore for secondary HLH, by clinical parameter

For the HScore calculator see <http://saintantoine.aphp.fr/score/>

Submissions should be made via our electronic submission system at <http://ees.elsevier.com/thelancet/>

COVID-19 pneumonia and elevated IL-6 in China (ChiCTR2000029765),⁹ Janus kinase (JAK) inhibition could affect both inflammation and cellular viral entry in COVID-19.¹⁰

All patients with severe COVID-19 should be screened for hyperinflammation using laboratory trends (eg, increasing ferritin, decreasing platelet counts, or erythrocyte sedimentation rate) and the HScore¹¹ (table) to identify the subgroup of patients for whom immunosuppression could improve mortality. Therapeutic options include steroids, intravenous immunoglobulin, selective cytokine blockade (eg, anakinra or tocilizumab) and JAK inhibition.

PM is a clinical training fellow within the Experimental Medicine Initiative to Explore New Therapies network and receives project funding unrelated to this Correspondence. PM also receives co-funding by the National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre. DFM chairs the NIHR and Medical Research Council funding committee for COVID-19 for therapeutics and vaccines. DFM reports personal fees from consultancy for ARDS for GlaxoSmithKline, Boehringer Ingelheim, and Bayer; in addition, his institution has received funds from grants from the UK NIHR, Wellcome Trust, Innovate UK, and others, all unrelated to this Correspondence. DFM also has a patent issued to his institution for a treatment for ARDS. DFM is a Director of Research for the Intensive Care Society and NIHR Efficacy and Mechanism Evaluation Programme Director. All other authors declare no competing interests.

Puja Mehta, Daniel F McAuley, Michael Brown, Emilie Sanchez, Rachel S Tattersall, *Jessica J Manson, on behalf of the HLH Across Speciality Collaboration, UK

jessica.manson@nhs.net

Centre for Inflammation and Tissue Repair, UCL Respiratory, Division of Medicine, University College London, London, UK (PM); Department of Rheumatology (JJM), Hospital for Tropical Diseases (MB), and Department of Clinical Virology (ES), University College London Hospital, London NW1 2PG, UK; Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, UK (DFM); Regional Intensive Care Unit, Royal Victoria Hospital, Belfast, UK (DFM); Department of Rheumatology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK (RST); and Sheffield Children's Hospital NHS Foundation Trust, Sheffield, UK (RST)

1 WHO. Coronavirus disease 2019 (COVID-19) situation report – 52. March 12, 2020. https://www.who.int/docs/default-source/coronaviruse/20200312-sitrep-52-covid-19.pdf?sfvrsn=e2bfc9c0_2 (accessed March 13, 2020).

- Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; published online March 3. DOI:10.1007/s00134-020-05991-x.
- Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet* 2014; **383**: 1503–16.
- Karakike E, Giamarellos-Bourboulis EJ. Macrophage activation-like syndrome: a distinct entity leading to early death in sepsis. *Front Immunol* 2019; **10**: 55.
- Sequin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. *Chest* 2016; **149**: 1294–301.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497–506.
- Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020; **395**: 473–75.
- Shakoory B, Carrillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase iii trial. *Crit Care Med* 2016; **44**: 275–81.
- Chinese Clinical Trial Registry. A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). Feb 13, 2020. <http://www.chictr.org.cn/showprojen.aspx?proj=49409> (accessed March 6, 2020).
- Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 2020; **395**: e30–31.
- Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014; **66**: 2613–20.

Did the hesitancy in declaring COVID-19 a pandemic reflect a need to redefine the term?

WHO's declaration that the global spread of coronavirus disease 2019 (COVID-19) is a pandemic¹ has contributed greatly to clearing up confusion in the terminology in the professional literature and the media. Discussions on when wide geographical spread of a disease becomes a pandemic tend to recur when the world is confronted with an emerging infectious disease.^{2,3} The debate around the terminology used for COVID-19 raises two important questions.

The first question is why there was reluctance to call the COVID-19 outbreak a pandemic, and the second question is whether the terminology is of any practical importance.

In almost all good textbooks, an epidemic becomes a pandemic when there is widespread geographical distribution of the disease. For some weeks, the COVID-19 epidemic, which had spread to over 100 countries, seemed to fit the classical definition of a pandemic. One could reasonably ask whether the use of the term pandemic would change any of the actions necessary to control the spread of the virus.

There are several situations in which it could be helpful to use well defined terminology to control the spread of an infectious disease. The resources for controlling a pandemic are both different, substantially larger, and generally much more far-reaching than for a localised outbreak or epidemic. Thus the terms used for the different situations could be restricted according to the control measures that are necessary. Perhaps unique to pandemics, these include considerable international coordination and collaboration in providing aid to affected countries, recruiting the necessary resources for promoting research on medications and vaccines, and developing complex risk communication. In particular, travel restrictions become a major issue and, although these are guided by the International Health Regulations, countries have the option to adopt unilaterally their own barriers to international travel. This was clearly the case for COVID-19. If the term pandemic is clearly defined, it can communicate much more clearly the seriousness of the situation and help justify the extreme measures instituted. It can also provide the international health community with a common term to enlist the cooperation of the general public and convey the necessary sense of urgency to decision makers. This should stimulate rapid



Published Online
March 12, 2020

[https://doi.org/10.1016/S0140-6736\(20\)30630-9](https://doi.org/10.1016/S0140-6736(20)30630-9)

For the **International Health Regulations** see <https://www.who.int/ihr/en/>