

## 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%,<sup>1</sup> 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.<sup>2</sup> 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 infections<sup>3</sup> and occurs in 3·7–4·3% of sepsis cases.<sup>4</sup> Cardinal features of sHLH include unremitting fever, cytopenias, and hyperferritinaemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients.<sup>5</sup> 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- $\gamma$  inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- $\alpha$ , and tumour necrosis factor- $\alpha$ .<sup>6</sup> 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 ( $p < 0\cdot0001$ ),<sup>2</sup> 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.<sup>7</sup>

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.<sup>8</sup> A multicentre, randomised controlled trial of tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), has been approved in patients with



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

The HScore<sup>‡</sup> 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.<sup>‡</sup> 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 mm<sup>3</sup> or less, or platelet count of 110 000 platelets per mm<sup>3</sup> 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/>

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COVID-19 pneumonia and elevated IL-6 in China (ChiCTR2000029765),<sup>9</sup> Janus kinase (JAK) inhibition could affect both inflammation and cellular viral entry in COVID-19.<sup>10</sup>

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 HScore<sup>11</sup> (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.

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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](https://www.who.int/docs/default-source/coronaviruse/20200312-sitrep-52-covid-19.pdf?sfvrsn=e2bfc9c0_2) (accessed March 13, 2020).

- 2 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.
- 3 Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet* 2014; **383**: 1503–16.
- 4 Karakike E, Giamarellos-Bourboulis EJ. Macrophage activation-like syndrome: a distinct entity leading to early death in sepsis. *Front Immunol* 2019; **10**: 55.
- 5 Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. *Chest* 2016; **149**: 1294–301.
- 6 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.
- 7 Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020; **395**: 473–75.
- 8 Shakoory B, Carcillo 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.
- 9 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).
- 10 Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet* 2020; **395**: e30–31.
- 11 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.