

Maintaining a clinical suspicion for secondary HLH and performing early bone marrow biopsy in patients presenting with hyperinflammatory features will support rapid life-saving treatment as in this case and IL-6 receptor antagonists provide an efficacious therapeutic option that is available in critical care units nationwide.

Acknowledgements

GS, KK, AR, TA, MD and AC made substantial contributions to writing the manuscript. We would like to thank the Intensive Care team at Milton Keynes University Hospital for their incredible dedication throughout the pandemic.

Conflict of interest

The authors declare no conflict of interest.

Gina Sangha¹ 

Kunaal Kaushik¹

Amelia Robinson²

Thomas Ainge²

Moez Dugarwalla²

Arup Chakraborty²

¹Oxford University Hospital NHS Foundation Trust, Oxford and ²Milton Keynes University Hospital, Milton Keynes, UK.

E-mail: arup.chakraborty@mkh.nhs.uk

Patient consent obtained.

Keywords: COVID-19, haemophagocytic syndrome, bone marrow morph

First published online 16 May 2021

doi: 10.1111/bjh.17533

References

- Wood H, Jones JR, Hui K, Mare T, Pirani T, Galloway J, et al. Secondary HLH is uncommon in severe COVID-19. *Br J Haematol*. 2020;**190**:e283–e285.
- Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;**395**:1033–4.
- Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet*. 2014;**383**:1503–16.
- La Rosée P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood*. 2019;**133**:2465–77.
- Hayden A, Park S, Giustini D, Lee AY, Chen LY. Hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) in adults: a systematic scoping review. *Blood Rev*. 2016;**30**:411–20.
- Henter J-I, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;**48**:124–31.
- Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol*. 2014;**66**:2613–20.
- Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? *J Transl Med*. 2020;**18**:164.
- Mudd PA, Crawford JC, Turner JS, Souquette A, Reynolds D, Bender D, et al. Distinct inflammatory profiles distinguish COVID-19 from influenza with limited contributions from cytokine storm. *Sci Adv*. 2020;**6**(50): eabe3024.
- RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;**384**:693–704.
- Horby PW, Pessoa-Amorim G, Peto L, Brightling CE, Sarkar R, Thomas K, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. *medRxiv*. 2021:2021.2002.2011.21249258.
- Deblquis A, Harzallah I, Mootien JY, Poidevin A, Labro G, Mejri A, et al. Haemophagocytosis in bone marrow aspirates in patients with COVID-19. *Br J Haematol*. 2020;**190**:e70–e73.
- Tan LI, Wang QI, Zhang D, Ding J, Huang Q, Tang Y-Q, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther*. 2020;**5**:33.
- Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med*. 2020;**8**:1233–44.
- Leverenz DL, Tarrant TK. Is the HScore useful in COVID-19? *Lancet*. 2020;**395**:e83.
- Paolucci S, Cassaniti I, Novazzi F, Fiorina L, Piralla A, Comolli G, et al. EBV DNA increase in COVID-19 patients with impaired lymphocyte subpopulation count. *Int J Infect Dis*. 2020;**104**:315–9.
- Lehner GF, Klein SJ, Zoller H, Peer A, Bellmann R, Joannidis M. Correlation of interleukin-6 with Epstein-Barr virus levels in COVID-19. *Crit Care*. 2020;**24**:657.
- Antonodimitrakis P, Wassberg C, Gerovasileiou S, Back J, Hallgren R, Olsen B. Fulminant hemophagocytic lymphohistiocytosis secondary to a reactivated EBV infection: a case report. *Upsala J Med Sci*. 2013;**118**:42–5.

Limited utility of the HScore in detecting secondary haemophagocytic lymphohistiocytosis in COVID-19: response

We initially responded¹ to the prior recommendations in the *Lancet* on screening with the HScore to guide immunosuppressive therapy in COVID-19 patients.² We identified that this is likely to be inappropriate due to the

differences in the COVID-19-related hyperinflammatory syndrome *versus* other alternate causes of secondary haemophagocytic lymphohistiocytosis (sHLH).¹ In this letter, Sangha *et al.* acknowledge that the HScore is not well

suiting to guide immunosuppressive therapy in COVID-19 patients.

Patients with severe COVID-19 do have a hyperinflammatory process, but it should not necessarily be regarded as sHLH — therefore the HLH 2004/HScore systems should not be used to determine treatment in this setting. We would contend that the decision on using dexamethasone and tocilizumab in severe COVID-19 should not be based on whether the patient meets previously defined criteria for secondary HLH and especially not on the presence or absence of haemophagocytosis in the bone marrow. Haemophagocytosis in itself is neither sensitive nor specific; any benefit of a bone marrow biopsy in the context of COVID-19 is more likely to come from ruling out other pathology. Additionally, bone marrow biopsies might introduce unnecessary delays in management and potential infective risk to operators/laboratory personnel who also deal with vulnerable haemato-oncology patients. Finally, trying to categorise SARS-CoV-2-related hyperinflammation according to old concepts is not necessarily a useful approach in the investigation and treatment of severe COVID-19, which should follow the national guidelines and clinical trials.

Henry Wood^{1,2} 

Austin G. Kulasekararaj^{1,2,3} 

¹Department of Haematological Medicine, King's College Hospital-NHS Foundation Trust, ²King's College London, London and ³NIHR/Wellcome King's Clinical Research Facility, London, UK.

E-mail: austin.kulasekararaj@nhs.net

Keywords: immunosuppressive therapy, COVID-19, hyperinflammatory syndrome

First published online 16 May 2021

doi: 10.1111/bjh.17535

References

1. Wood H, Jones JR, Hui K, Mare T, Pirani T, Galloway J, et al. Secondary HLH is uncommon in severe COVID-19. *Br J Haematol.* 2020;**190**(5):e283–e285.
2. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* 2020;**395**(10229):1033–4.