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.

and headache. He described a transient maculopapular palmar rash 4 days into illness (appendix pp 3–4). He had non-exudative conjunctivitis, cervical lymphadenopathy, cracked lips, and prominent lingual papillae (appendix pp 3–4). A CT scan showed mesenteric adenopathy and terminal ileitis. The patient had neutrophilia, eosinophilia, lymphopenia, elevated inflammatory markers, and elevated troponin T with normal electrocardiogram, transthoracic echocardiogram, and CT coronary angiogram (appendix pp 2–3).

The patient had no previous history of COVID-19 symptoms or contact with known COVID-19 cases. Nasopharyngeal and stool samples were negative for SARS-CoV-2 by PCR. Other infective and inflammatory conditions were excluded (appendix p 2). Adult and paediatric specialists conferred and concluded that the most likely diagnosis was Kawasaki-like disease on the PIMS-TS spectrum. The patient was treated with intravenous immunoglobulin and methylprednisolone, which resulted in rapid resolution of symptoms and normalisation of blood parameters (appendix p 3); he was discharged on low-dose aspirin 8 days after admission to hospital.

SARS-CoV-2 serology[3] (checked before treatment with intravenous immunoglobulin) was strongly positive, suggesting recent exposure to SARS-CoV-2 (appendix p 2). Kawasaki disease has been described in adults in association with viral infection.[4,5] To the best of our knowledge, this is the first reported case of adult Kawasaki-like disease related to SARS-CoV-2 infection. There is an urgent need to recognise and fully characterise PIMS-TS in young adults to improve our understanding of pathogenesis, guide treatment decisions, and prevent sequelae in these patients.

We declare no competing interests. We acknowledge support from colleagues at Great Ormond Street Hospitals, London, including Louis Grandjean and Charalampia Papadopoulou. Members of the UCLH COVID Response Team include Mike Brown, Tom Parks, Alice Armitage, Li-An Brown, Manik Kohli, Corinne Fisher, Catherine Houlihan, Hannah Rickman, and Tommy Rampling.

*Imogen Jones, *Lucy C K Bell, Jessica J Manson, Anna Last, on behalf of the UCLH COVID Response Team*
lucy.bell7@nhs.net

Hospital for Tropical Diseases, University College London Hospitals, London W1T 7DN, UK (IJ, LCKB, AL); and Department of Rheumatology, University College London Hospitals, London, UK (JJM)

1 Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; **395:** 1607–08.
2 Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020; **395:** 1771–78.
3 Ng K, Faulkner N, Cornish G, et al. Pre-existing and de novo humoral immunity to SARS-CoV-2 in humans. *bioRxiv* 2020; published online May 15. https://doi.org/10.1101/2020.05.14.095414 (preprint).
4 Drago F, Javor S, Ciccarese G, Cozzani E, Parodi A. A case of complete adult-onset Kawasaki disease: a review of pathogenesis and classification. *Dermatology* 2015; **231:** 5–8.
5 Stankovic K, Miailhes P, Bessis D, Ferry T, Broussolle C, Sève P. Kawasaki-like syndromes in HIV-infected adults. *J Infect* 2007; **55:** 488–94.

Intravenous anakinra for cytokine storm syndromes

In their Viewpoint on cytokine storm syndromes, Puja Mehta and colleagues[1] stated that "there is a critical need and growing call for unified nomenclature (such as cytokine storm syndromes)". Although we agree that a multidisciplinary effort is needed to analyse and classify these conditions, we have concerns about unifying them all under a single umbrella. Indeed, cytokine storm syndromes currently encompass several different conditions with extremely varied causes, pathophysiological processes, or prominant cytokines. Although they manifest with similar symptoms, they might have only one truly common feature: hypercytokinaemia.

For instance, haemophagocytic lymphohistiocytosis might be the consequence of deficient cytotoxic cells (primary and some virally-induced haemophagocytic lymphohistiocytosis),[2] hyperactivation of the inflammasome pathway (NLRC4-associated macrophage activation syndrome),[3] or a yet-to-be-defined combination of these factors (eg, Still's disease spectrum). All of these conditions are characterised by elevated plasma concentrations of IL-1 family cytokines (IL-1β and IL-18) and tissue haemophagocytosis. Alternatively, cytokine release syndrome secondary to chimeric antigen receptor T-cell therapy has been linked to high IFN-γ release, whereas the involvement of the IL-1 family cytokines seemed less prominent.[4] Lastly, it is noteworthy that cytokine storm has attracted great interest, as a result of its description as a major determinant of COVID-19 outcomes. Yet, despite there being no definitive understanding of its immunopathology, a hallmark of COVID-19-associated cytokine storms seems to be prominent IL-6 elevation, with only 25% of patients showing evidence for IL-1-driven macrophage activation or haemophagocytosis.[5] In the remaining 75% of patients, the disease has been compared with complex immune dysregulation seen in patients with sepsis (ie, prominent role for IL-6, low HLA-DR expression, and lymphopenia).

These considerations are important because the clinicians' armamentarium is now large enough to offer the best targeted therapies in these different contexts (ie, inhibitors of IL-1, IFN-γ, or IL-6). Defining criteria for choosing one treatment over the other, or instead of a less-targeted therapy (eg, corticosteroids or Janus kinase inhibitors) will certainly be one of the challenges of clinical trials in the near future.

Overall, we suggest that if an international, multidisciplinary effort is mounted to unify cytokine storm syndromes within one spectrum, this nomenclature will have to be subdivided on the basis of the cause, the supposed pathophysiology, and

See Online for appendix

Published Online July 21, 2020 https://doi.org/10.1016/S2665-9913(20)30225-3

the pivotal cytokines involved. In daily practice, the availability of rapid immune monitoring tests (eg, cytokine multiplex assays) would therefore be of utmost interest.

We declare no competing interests.

See Online for appendix

*Yvan Jamilloux,
Mathieu Gerfaud-Valentin, Pascal Sève
yvan.jamilloux@chu-lyon.fr

Department of Internal Medicine, Hopital de la Croix-Rousse, Hospices Civils de Lyon, F-69004 Lyon, France (YJ, MG-V, PS); and Inserm U1111, CIRI, Université Claude Bernard Lyon 1, Lyon, France (YJ)

1 Mehta P, Cron R, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol* 2020; **2:** e358–67.
2 Carter SJ, Tattersall RS, Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. *Rheumatology (Oxford)* 2019; **58:** 5–17.
3 Canna SW, de Jesus AA, Gouni S, et al. An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. *Nat Genet* 2014; **46:** 1140–46.
4 Dholaria BR, Bachmeier C, Locke F. Mechanisms and management of chimeric antigen receptor T-cell therapy related toxicities. *BioDrugs Clin Immunother Biopharm Gene Ther* 2019; **33:** 45–60.
5 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.

Published Online
July 21, 2020
https://doi.org/10.1016/S2665-9913(20)30219-8

We read with interest the Viewpoint by Puja Mehta and colleagues[1] on the use of intravenous anakinra in secondary haemophagocytic lymphohistiocytosis or macrophage activation syndrome (sHLH/MAS), in which they suggest a framework for the management of cytokine storm syndromes.

As clinical immunologists who collaborate daily with intensivists, our primary concern, not unlike that of Mehta and colleagues,[1] is the causal diagnosis of sHLH/MAS. Unlike Mehta and colleagues, however, we find it difficult not to separate subclinical hyperinflammatory states with some macrophage activation syndrome features from macrophage activation syndrome that requires intensive care, because their treatment objectives are simply not the same. A stepwise approach with corticosteroids as first-line therapy would have the added benefit of selecting a second-line treatment on the basis of clinical context and disease severity. We provide a tentative approach to treating sHLH/MAS in the appendix that reflects this philosophy and also incorporates the framework suggested by Mehta and colleagues.

From a purely rheumatological point of view, anakinra seems like an appealing treatment for macrophage activation syndrome triggered by systemic autoimmune or autoinflammatory diseases and even, off label, for highly inflammatory states resulting from infectious triggers.[1] However, systemic autoimmune diseases make up barely a quarter of the overall causes of macrophage activation syndrome.[2] Anakinra is not the best first-line treatment when specific drug combination therapies with sufficiently anti-inflammatory and immunosuppressive effects on cytokine storm are indicated (ie, for lymphoma).

The risk of clinical worsening after immunosuppressive therapy for macrophage activation syndrome caused by parasitic infections must also be emphasised. For instance, in vitro and in vivo findings from a mouse model suggested that NLRP3 inflammasome activation and IL-1β signalling are required for elimination of *Leishmania* infection.[3,4] In the clinic, leishmaniasis-associated macrophage activation syndrome can be fatal, and the risk of death is increased by the inappropriate use of steroids or immunosuppressive agents in patients with undiagnosed parasitic infection. These cases are occasional and are insufficiently described in the literature.[5]

Although we sincerely hope that anti-IL-1 receptor antagonists would provide a survival benefit over current therapeutics (eg, steroids and etoposide), evidence for this benefit is still missing, as Mehta and colleagues themselves point out. For reasons provided earlier, anakinra seems more suited for treating macrophage activation syndrome-associated diseases with systemic autoimmune or autoinflammatory causes, pending increased knowledge of its potential effects on viral infections.

Future clinical trials involving anakinra for the treatment of macrophage activation syndrome need to focus on more specific groups of patients, both in terms of underlying causes of the condition and disease severity.

We declare no competing interests.

*Nihal Martis,
Alexandra Audemard-Verger
martis.n@chu-nice.fr

Medical Intensive Care Unit and Internal Medicine Department, University Hospital of Nice, 06200 Nice, France (NM); Côte d'Azur University, Nice, France (NM); Internal Medicine Department, University Hospital of Tours, Tours, France (AA-V); and University of Tours, Tours, France (AA-V)

1 Mehta P, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. *Lancet Rheumatol* 2020; **2:** e358–67.
2 Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet* 2014; **383:** 1503–16.
3 Chaves MM, Sinflorio DA, Thorstenberg ML, et al. Non-canonical NLRP3 inflammasome activation and IL-1β signaling are necessary to L. amazonensis control mediated by P2X7 receptor and leukotriene B4. *PLoS Pathog* 2019; **15:** e1007887.
4 Kautz-Neu K, Kostka SL, Dinges S, Iwakura Y, Udey MC, von Stebut E. A role for leukocyte-derived IL-1RA in DC homeostasis revealed by increased susceptibility of IL-1RA-deficient mice to cutaneous leishmaniasis. *J Invest Dermatol* 2011; **131:** 1650–59.
5 Koné-Paut I, Retornaz K, Garnier JM, Bader-Meunier B. Visceral leishmaniasis in a patient with systemic juvenile arthritis treated by IL-1RA agonist (anakinra). *Clin Exp Rheumatol* 2007; **25**: 119.

Published Online
July 21, 2020
https://doi.org/10.1016/S2665-9913(20)30215-0

Authors' reply

We appreciate the interest in our Viewpoint[1] on the use of intravenous anakinra in cytokine storm syndromes. Yvan Jamilloux and colleagues contribute to continuing discussions regarding the terminology of hyperinflammatory disorders;[2] we suggest a unifying umbrella term of cytokine storm syndromes. We feel that it is the concept of hyperinflammation