Commentary *Highlight article*

Secondary hemophagocytic lymphohistiocytosis versus cytokine release syndrome in severe COVID-19 patients

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Impact statement

Severe COVID-19 associated pneumonia and acute respiratory distress syndrome has recently been described with life-threatening features of cytokine storm and loosely referred to as hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS). Although a recent report indicated favorable responses to the interleukin-1 receptor antagonist, anakinra in eight patients with COVID-19 secondary HLH diagnosed using the HScore calculation, others have suggested that the diagnosis of secondary HLH is uncommon and that the use of the HScore has limited value in guiding immunomodulatory therapy for COVID-19. Here, we provide additional perspective on this important controversy based upon comparisons between 14 COVID-19 cytokine storm patients and 10 secondary HLH patients seen immediately prior to the pandemic. We hypothesize that identification of HLH may relate to the severity or timing of cytokine release and suggest distinguishing between cytokine release syndrome and secondary HLH, reserving the latter term for cases fulfilling diagnostic criteria.

Abstract

COVID-19 or SARS-CoV-2 infection can lead to severe acute respiratory distress syndrome/pneumonia with features of cytokine storm reminiscent of secondary hemophagocytic lymphohistiocytosis (HLH), which can be diagnosed by the calculated HScore. Recent reports have suggested favorable responses to the interleukin-1 receptor antagonist, anakinra in patients with COVID-19 associated secondary HLH. In our single institution study, we compared 14 COVID-19 cytokine storm patients with 10 secondary HLH patients seen immediately prior to the pandemic (non-COVID-19), to determine whether diagnostic features of secondary HLH were typically seen in COVID-19 patients presenting with cytokine storm. Although most of our COVID-19 patients did not fulfill diagnostic criteria for HLH, we hypothesize that identification of HLH may relate to the severity or timing of cytokine release. Based on our observations, we would suggest distinguishing between cytokine release syndrome and secondary HLH, reserving the latter term for cases fulfilling diagnostic criteria.

Keywords: Cytokines, immunology/microbiology/virology, inflammation, COVID-19

***Experimental Biology and Medicine* 2021; 246: 5–9. DOI: 10.1177/1535370220962043**

COVID-19 or SARS-CoV-2 infection can lead to severe acute respiratory distress syndrome (ARDS)/pneumonia with features of cytokine storm reminiscent of secondary hemophagocytic lymphohistiocytosis (HLH),[1] which can be diagnosed by the calculated HScore.[2] A recent report has suggested that the diagnosis of secondary HLH in severe COVID-19 patients is uncommon and that the use of the HScore has limited value in guiding immunomodulatory therapy.[3] In contrast, Dimopoulos *et al*.[4] reported favorable responses to the interleukin-1 receptor antagonist, anakinra in 8 patients with COVID-19 associated secondary HLH as diagnosed by HScore. Anakinra has also been reported to lead to clinical improvement in two cohort studies of COVID-19 patients with ARDS and hyperinflammation but not specifically diagnosed with HLH.[5,6] Here we provide additional perspective on this controversy based upon

comparisons between 14 COVID-19 cytokine storm patients with 10 secondary HLH patients seen immediately prior to the pandemic.

Severe COVID-19 pneumonia with ARDS has been described to lead to systemic hyperinflammation reminiscent of secondary HLH or macrophage activation syndrome (MAS).[1] Profiling of cases has documented evidence of a cytokine storm, with elevated interferon gamma-induced protein 10 (IP-10), monocyte chemotactic protein 3 (MCP-3), and IL-1 receptor antagonist (IL-1ra) associated with disease severity and fatality.[7] Laboratory parameters such as C-reactive protein and ferritin can be markedly elevated, and abnormal liver function and coagulopathy can be seen. Elevation of D-dimer levels and abnormal coagulation profiles consistent with disseminated intravascular coagulation (DIC) are seen and may be indicative of pulmonary microthrombi.[8,9] Some investigators have suggested that the immune mechanism in COVID-19 cytokine storm may be related to virally induced immunosuppression and NK cell dysfunction.[10,11]

The HScore can be easily calculated to help include or exclude HLH from the differential diagnosis,[2] and a cutoff of 168 showed 100% sensitivity and 94.1% specificity for HLH in a large cohort of critically ill adult patients.[12] The scoring system considers an array of standard laboratory tests such as ferritin, LDH, triglycerides, liver enzymes, degree of cytopenia, imaging findings, and bone marrow biopsy results to assess the likelihood of HLH and was used to describe a series of 8 COVID-19 patients presenting with secondary HLH and responding partially to anakinra.[4] Following treatment, these ICU patients had less need for vasopressors, significantly improved respiratory function, lower HScore, and a lower mortality than in a historical series of secondary HLH patients in sepsis. However, this study did not specifically indicate the relative frequency of diagnosed HLH in their COVID-19 cytokine storm population. Wood *et al*.[3] reported that secondary HLH was diagnosed (with HScore >169) in only 3 of 40 (7.5%) severe COVID-19 patients treated at their single center intensive care units.

In our single institution study, we compared 14 COVID-19 cytokine storm patients with 10 secondary HLH patients seen immediately prior to the pandemic, to determine whether diagnostic features of secondary HLH were typically seen in COVID-19 patients presenting with cytokine storm. Our COVID-19 case series was established with the help of the Northwell Health COVID-19 Research Consortium. The Northwell Health Institutional Review Board approved this case series as minimal-risk research using data collected for routine clinical practice and waived the requirement for informed consent. The initial characteristics of 5700 patients from Northwell are presented elsewhere,[13] and this case series presents in-depth hematology results not presented in that article.

Table 1 compares the clinical demographics of 14 patients with COVID-19 associated cytokine storm with 10 non-COVID-19 secondary HLH patients in Table 2. All 14 COVID-19 patients had severe disease as defined by a high requirement for supplemental oxygen or ventilatory support. They all exhibited signs of a hyperinflammatory state with markedly elevated ferritin and C-reactive protein levels. The putative etiologies of secondary HLH for the 10 non-COVID-19 patients were varying and reflected known associations with malignancies and infections, predominantly. Table 3 compares the HScores of the COVID-19 patients with those of non-COVID-19 patients in Table 4. The 10 non-COVID-19 patients all had HScore calculations well above the cutoff of 168 and suggesting at least 70 to 80% probability of HLH. By contrast, cytopenia and hepatosplenomegaly were mostly absent in our COVID-19 patients. Consequently, HScore calculations generally indicated low probabilities of HLH, with the exception being Case 1, Table 3. Of interest, this HLH patient was also the youngest in our cohort, which ranged from 37 to 88 years of age (Table 1). He was treated with tocilizumab and had a significant drop in ferritin, C-reactive protein, and D-Dimer (with decreased HScore) following therapy but eventually expired on ventilator therapy.

Our observations suggest several themes, which remain to be confirmed with larger studies. First, as described by Wood *et al*.,[3] most of our patients with COVID-19 cytokine

Table 1. Demographics and clinical information for COVID 19 patients with severe cytokine storm.

Pt	Age (y)	Sex	Co-morbidities	Clinical symptoms	O_2 requirements
1	37	M	None	Fever, cough, SOB	Intubation
2	88	F	HTN, HLD, asthma, hypothyroidism, colon cancer	SOB	15L NRB
3	51	M	Asthma, HTN, HLD	Fever, SOB	15L NRB
4	62	F	DM2, asthma, liver transplant	WOB	15L NRB
5	57	M	None	SOB	Intubation
6	64	M	None	SOB, cough	Intubation
7	58	M	HTN, HLD	Cough, SOB, chills	15L NRB
8	81	M	HTN, DM2, GERD, pancreatitis	Fevers, cough, chills, diarrhea	15L NRB
9	74	F	HTN, DM2, CAD	Chills, cough, SOB	Intubation
10	65	F	DM2	Cough, chills	Intubation
11	51	F	Schizophrenia, breast cancer	Fever, malaise	Intubation
12	79	F	DM2, HLD, hyperthyroidism, Afib, HTN	SOB	Intubation
13	52	M	HTN, HLD, hypothyroidism	SOB	Intubation
14	46	M	DM2, HTN, OSA	SOB	Intubation

HTN: hypertension; HLD: hyperlipidemia; DM2: type 2 diabetes mellitus; GERD: gastro-esophageal reflux disease; CAD: coronary artery disease; Afib: atrial fibrillation; OSA: obstructive sleep apnea; SOB: shortness of breath; WOB: work of breathing; NRB: non-rebreather.

Table 2. Demographics and clinical information for HLH patients.

Pt	Age (y)	Sex	Co-morbidities	Clinical symptoms	Putative etiology of HLH
1	78	M	DM2	Hematuria, jaundice, fatigue, fever, chills	Anaplastic lymphoma
2	79	F	MDS	Lethargy, unresponsiveness, fever	Chemotherapy induced
3	70	F	HTN, OSA	Fever, RLE rash, edema	NK cell lymphoma
4	20	M	n/a	Fever, abdominal pain, nausea, vomiting, rash, neck pain	Idiopathic/unproved viral?
5	63	M	Cirrhosis, HTN, HLD	Fever	Idiopathic
6	22	F	Bipolar disorder	Fever	Anaplastic lymphoma/EBV
7	84	M	HTN, CAD	Fever, confusion	CLL/EBV
8	76	M	HTN, HLD	Fever, fatigue	Flu vaccine
9	35	F	n/a	Fever	Pregnancy
10	48	M	ETOH abuse, Crohn's disease	Fever, cough, SOB, weight loss, fatigue	NK cell leukemia

HLH: hemophagocytic lymphohistiocytosis; DM2: type 2 diabetes mellitus; MDS: myelodysplastic syndrome; HTN: hypertension; OSA: obstructive sleep apnea; HLD: hyperlipidemia; CAD: coronary artery disease; ETOH: alcohol; RLE: right lower extremity; SOB: shortness of breath; NK: natural killer; EBV: Epstein Barr virus; CLL: chronic lymphocytic leukemia/lymphoma.

Table 3. HScores of 14 COVID-19 patients with severe cytokine storm.

Pt	T (F)	Organo-megaly	Lines of cytopenia	TG (mg/dL)	Fibrinogen (mg/dL)	Ferritin (mcg/L)	AST (IU/L)	Immune-suppression	Hemo-phagocytosis	Hscore (Prob HLH)	Outcome
1	101.8 (33)	+ (38)	Hb 7.7 g/dL (0)	588 (64)	433 (0)	13979 (50)	39 (19)	None (0)	N/A	204 (88–93%)	Expired
2	98.7 (0)	N/A	None (0)	N/A	N/A	451 (0)	30 (19)	None (0)	N/A	19 (<1%)	Recovered
3	98.9 (0)	N/A	None (0)	N/A	N/A	486 (0)	36 (19)	None (0)	N/A	19 (<1%)	Recovered
4	99.4 (0)	N/A	None (0)	N/A	N/A	5931 (35)	41 (19)	yes (18)	N/A	72 (<1%)	Recovered
5	98.7 (0)	N/A	None (0)	N/A	N/A	1176 (0)	70 (19)	None (0)	N/A	19 (<1%)	Expired
6	97.2 (0)	N/A	PLT 102×10^9/L (0)	77 (0)	661 (0)	2274 (35)	92 (19)	None (0)	N/A	54 (<1%)	Expired
7	98.4 (0)	N/A	Hb 8.1 g/dL (0)	166 (44)	810 (0)	1729 (0)	78 (19)	None (0)	N/A	63 (<1%)	Recovered
8	98.7 (0)	N/A	None (0)	80 (0)	N/A	1725 (0)	107 (19)	None (0)	N/A	19 (<1%)	Expired
9	97.7 (0)	N/A	None (0)	1478 (64)	825 (0)	2834 (35)	25 (0)	None (0)	N/A	99 (~1%)	Expired
10	98.2 (0)	N/A	None (0)	N/A	805 (0)	893 (0)	39 (19)	None (0)	N/A	19 (<1%)	Expired
11	103 (49)	− (0)	PLT 81×10^9/L (0)	132 (0)	900 (0)	1544 (0)	68 (19)	None (0)	N/A	68 (<1%)	Expired
12	100.9 (0)	− (0)	None (0)	99 (0)	792 (0)	540 (0)	74 (19)	None (0)	N/A	19 (<1%)	Expired
13	98.1 (0)	− (0)	None (0)	763 (64)	853 (0)	736 (0)	172 (19)	None (0)	N/A	83 (<1%)	Recovered
14	100.2 (0)	− (0)	None (0)	467 (64)	375 (0)	736 (0)	35 (19)	None (0)	N/A	83 (<1%)	Expired

Note: Numbers in brackets refer to the points allocated per score variable.
HLH: hemophagocytic lymphohistiocytosis; TG: triglycerides; AST: aspartate aminotransferase; Hb: hemoglobin; PLT: platelet count; N/A: not available; WBC: total white blood cell count; Prob HLH: probability of HLH.

storm did not fulfill diagnostic criteria for HLH. This was most commonly due to absence of cytopenia or hepatosplenomegaly or hypofibrinogenemia, but also because levels of ferritin or temperature elevation did not reach criteria. Hemophagocytosis could not be assessed as bone marrow biopsy was not performed (also not done in the Dimopoulos series[4] and not found in the single patient who underwent biopsy in the Wood series of 40 patients[3]). However, hemophagocytosis is not an obligate diagnostic criterion, and even if present, would not have added a numerical HScore value sufficient for diagnosis of HLH in any of our patients (Table 3). A recent small autopsy series of four COVID-19 patients with diffuse alveolar damage within the lungs demonstrated hemophagocytosis within pulmonary lymph nodes, but none had hemophagocytosis in liver or bone marrow.[14] HScores indicated either probable or likely HLH in two of the four patients.

Wood *et al*.[3] concluded that the HScore has limited value in guiding immunomodulatory therapy. However, Dimopoulos *et al*.[4] not only used the HScore to identify eight Greek/Dutch patients with secondary HLH but noted a decrease in the HScore following therapy with anakinra, suggesting a correlation with the degree of hyperinflammation. Our data also suggest that diagnostic criteria for HLH are usually not met in COVID-19 patients with cytokine storm. However, we suggest that the significance of secondary HLH is still undefined at present and warrants further investigation. Bindoli *et al*.[15] hypothesized that increasing amounts of cytokine release may define the severity of SARS-Cov2 infection with a spectrum ranging from mild disease to cytokine release syndrome to secondary HLH. As the HScore assigns a point value to clinical criteria that positively correlates with HLH diagnosis, it may separate mild and moderate hyperinflammation from critical HLH-like syndromes characterized by multiorgan failure.

As cytokine storm and secondary HLH in COVID-19 patients may represent a spectrum of the disease, immunomodulatory drugs such as IL-1 or IL-6 receptor antagonists may be of benefit in patients with severe forms of COVID-19.[5,6,16,17] Anakinra is an IL-1 receptor antagonist (IL-1ra) approved for rheumatoid arthritis and neonatal onset multisystem inflammatory disease (NOMID). Prior to the SARS-COV-2 pandemic, anakinra was shown to improve

Table 4. HScores of 10 HLH patients.

Pt	T (F)	Organo-megaly	Lines of cytopenia	TG (mg/dL)	Fibrinogen (mg/dL)	Fibrinogen (mg/dL)	AST (IU/L)	Immuno-supression	Hemo-phagocytosis	Hscore (Prob HLH)	Outcome
1	102.6 (33)	− (0)	2 (24)	320 (44)	100 (30)	46567 (50)	396 (19)	None (0)	Yes (35)	235 (98–99%)	Recovered
2	102.9 (33)	− (0)	2 (24)	296 (44)	419 (0)	10468 (50)	151 (19)	Yes (18)	None (0)	188 (70–80%)	Expired
3	104.7 (49)	− (0)	1 (0)	425 (64)	691 (0)	8396 (50)	22 (0)	Yes (18)	Yes (35)	216 (93–96%)	Expired
4	103.5 (49)	− (0)	2 (24)	391 (64)	675 (0)	10250 (50)	155 (19)	None (0)	Yes (35)	241 (>99%)	Recovered
5	102.3 (33)	+ (23)	2 (24)	112 (0)	890 (0)	12385 (50)	44 (19)	None (0)	Yes (35)	184 (70–80%)	Recovered
6	98.8 (0)	− (0)	1 (0)	423 (64)	120 (30)	3541 (35)	38 (19)	None (0)	Yes (35)	183 (70–80%)	Expired
7	101.8 (33)	+ (23)	3 (34)	158 (44)	184 (30)	19119 (50)	82 (19)	Yes (18)	Yes (35)	286 (>99%)	Expired
8	102.9 (33)	− (0)	2 (24)	519 (64)	950 (0)	7396 (50)	15 (0)	None (0)	Yes (35)	206 (88–93%)	Recovered
9	102.9 (33)	− (0)	0 (0)	507 (64)	408 (0)	4300 (35)	291 (19)	None (0)	Yes (35)	186 (70–80%)	Recovered
10	101.5 (33)	+ (23)	3 (34)	200 (64)	73 (30)	12343 (50)	302 (19)	None (0)	Yes (35)	288 (>99%)	Expired

Note: Numbers in brackets refer to the points allocated per score variable.
HLH: hemophagocytic lymphohistiocytosis; TG: triglycerides; AST: aspartate aminotransferase; Hb: hemoglobin; PLT: platelet count; N/A: not-available; WBC: total white blood cell count; Prob HLH: probability of HLH.

survival, when used in combination with IVIG and steroids, in classical secondary HLH patients in the ICU setting.[18,19] In patients with severe COVID-19, anakinra was also associated with clinical improvement in two recent prospective[6] and retrospective[5] cohort studies. However, neither of these two studies distinguished HLH from cytokine storm, and these trials should be compared with that of Dimopoulos *et al*.[4] using anakinra in defined HLH patients.

Based on our observations, we would suggest distinguishing between cytokine release syndrome and secondary HLH, reserving the latter term for cases fulfilling diagnostic criteria. We suggest this may have value in subset analysis of clinical trials of drugs such as anakinra[4] or tocilizumab[20] used to treat COVID-19 patients; patients with diagnostic criteria for HLH may behave differently from those with cytokine release syndrome but not meeting criteria for HLH.

Finally, we and others[3,4] have confirmed that certain COVID-19 patients do fulfill classical HLH diagnostic criteria and have an HScore suggesting high probability of disease. A recent autopsy series has also demonstrated hemophagocytosis within pulmonary lymph nodes in three of four cases.[14] What is the significance of HLH in COVID-19? To answer this, we need to learn much more about the natural history, clinical course, and immunologic basis of COVID-19 HLH. For example, our COVID-19 HLH patient was the youngest in our cohort, contradicting the assumption that hyperinflammatory syndromes might be more common in older adults. The immune basis of COVID-19 HLH may also differ with non-COVID-19 secondary HLH (as seen in our case series in Table 2). HLH is typically categorized into primary and secondary subtypes. The primary subtype is caused by biallelic genetic mutations that lead to cytotoxicity defects in T and NK cell function, whereas secondary HLH can be incited by infections, malignancies, rheumatologic, or autoimmune disorders. Non-COVID-19 secondary HLH patients do not have an NK cell cytotoxicity defect seen in primary HLH but rather an activated NK phenotype profile associated with decreased interferon gamma production.[21] Immune mechanisms in COVID-19 associated HLH may actually bear greater similarity to those in primary than secondary HLH: SARS-CoV-2 may directly impact NK cell cytotoxicity,[11] perhaps from binding to ACE2, which is expressed on NK cells.[22] The role of unrecognized genetic mutations or sequence variants analogous to those seen in primary HLH needs further study and may identify a population at particular risk for COVID-19 associated HLH.

Authors' contributions: NNH, CO, JC collected the data and with JML, wrote and edited the manuscript.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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REFERENCES

1. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the`cytokine storm' in COVID-19. *J Infect* 2020;**80**:607–13
2. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, Coppo P, Hejblum G. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014;**66**:2613–20
3. Wood H, Jones J, Hui K, Mare T, Pirani T, Galloway J, Metaxa V, Benjamin R, Rutherford A, Cain S, Kulasekararaj AG. Secondary HLH is uncommon in severe COVID-19. *Br J Haematol* 2020;**190**: e283–e285
4. Dimopoulos G, de Mast Q, Markou N, Theodorakopoulou M, Komnos A, Mouktaroudi M, Netea MG, Spyridopoulos T, Verheggen Rj Hoogerwerf J, Lachana A, van de Veerdonk FL, Giamarellos-Bourboulis EJ. Favorable anakinra responses in severe covid-19 patients with secondary hemophagocytic lymphohistiocytosis. *Cell Host Microbe* 2020; **28**:117–123
5. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, Oltolini C, Castiglioni B, Tassan Din C, Boffini N, Tomelleri A, Farina N, Ruggeri A, Rovere-Querini P, Di Lucca G, Martinenghi S, Scotti R,

Tresoldi M, Ciceri F, Landoni G, Zangrillo A, Scarpellini P, Dagna L. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020;**2**:e325–e31

6. Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, Sacco E, Naccache J-M, Bézie Y, Laplanche S, Le Berre A, Le Pavec J, Salmeron S, Emmerich J, Mourad J-J, Chatellier G, Hayem G. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020;**2**: e393–e400
7. Vaninov N. In the eye of the COVID-19 cytokine storm. *Nat Rev Immunol* 2020;**20**:277
8. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, Mucheli SS, Kuperan P, Ong KH. Hematologic parameters in patients with COVID-19 infection. *Am J Hematol* 2020;**95**:E131–4
9. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020;**18**:844–7
10. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation Syndrome-Like disease. *Autoimmun Rev* 2020;**19**:102537
11. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, Xu Y, Tian Z. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol* 2020;**17**:533–5
12. Knaak C, Nyvlt P, Schuster FS, Spies C, Heeren P, Schenk T, Balzer F, La Rosee P, Janka G, Brunkhorst FM, Keh D, Lachmann G. Hemophagocytic lymphohistiocytosis in critically ill patients: diagnostic reliability of HLH-2004 criteria and HScore. *Crit Care* 2020;**24**:244
13. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, The Northwell C-RC, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. *JAMA* 2020;**323**:2052–2059
14. Prilutskiy A, Kritselis M, Shevtsov A, Yambayev I, Vadlamudi C, Zhao Q, Kataria Y, Sarosiek SR, Lerner A, Sloan Jm Quillen K. Burks Ej SARS-CoV-2 Infection-Associated hemophagocytic lymphohistiocytosis. *Am J Clin Pathol* 2020;**154**:466–474
15. Bindoli S, Felicetti M, Sfriso P, Doria A. The amount of cytokine-release defines different shades of Sars-Cov2 infection. *Exp Biol Med* 2020;**245**:970–976
16. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, Franceschini E, Cuomo G, Orlando G, Borghi V, Santoro A, Gaetano M, Puzzolante C, Carli F, Bedini A, Corradi L, Fantini R, Castaniere I, Tabbi L, Mussini C. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatology* 2020; **2**:e474–e484
17. Biran N, Ip A, Ahn J, Go RC, Wang S, Mathura S, Sinclaire BA, Bednarz U, Marafelias M, Hansen E, Siegel DS, Goy AH, Pecora AL, Sawczuk IS, Koniaris LS, Simwenyi M, Varga DW, Tank LK, Stein AA, Allusson V, Lin GS, Oser WF, Tuma RA, Reichman J, Brusco L, Carpenter KL, Costanzo EJ, Vivona V, Goldberg SL. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. *Lancet Rheumatol* 2020; doi:10.1016/S2665-9913(20)30277-0
18. Wohlfarth P, Agis H, Gualdoni GA, Weber J, Staudinger T, Schellongowski P, Robak O. Interleukin 1 receptor antagonist anakinra, intravenous immunoglobulin, and corticosteroids in the management of critically ill adult patients with hemophagocytic lymphohistiocytosis. *J Intensive Care Med* 2019;**34**:723–31
19. Eloseily EM, Weiser P, Crayne CB, Haines H, Mannion ML, Stoll ML, Beukelman T, Atkinson TP, Cron RQ. Benefit of anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. *Arthritis Rheumatol* 2020;**72**:326–34
20. Zhang X, Song K, Tong F, Fei M, Guo H, Lu Z, Wang J, Zheng C. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Adv* 2020;**4**:1307–10
21. Carvelli J, Piperoglou C, Farnarier CC, Vely F, Mazodier K, Audonnet S, Nitschke P, Bole-Feysot C, Boucekine M, Cambon A, Hamidou M, Harle Jr de Saint Basile G, Kaplanski G. Functional and genetic testing in adults with HLH do not reveal a cytotoxicity defect but rather an inflammatory profile. *Blood* 2020;**136**:542–552
22. Rivellese F, Prediletto E. ACE2 at the Centre of COVID-19 from paucisymptomatic infections to severe pneumonia. *Autoimmun Rev* 2020;**19**:102536

(Received June 16, 2020, Accepted September 7, 2020)