Could hemophagocytic lymphohistiocytosis be the core issue of severe COVID-19 cases?

Violetta Opoka-Winiarska 1*, Ewelina Grywalska 2,3 and Jacek Rolinski 2,3

Abstract

Background: COVID-19, a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), commonly presents as fever, cough, dyspnea, and myalgia or fatigue. Although the majority of patients with COVID-19 have mild symptoms, some are more prone to serious outcomes, including pneumonia, acute respiratory distress syndrome (ARDS), and even death. Hemophagocytic lymphohistiocytosis (HLH) is a severe, life-threatening inflammatory syndrome associated with intense cytokine release (also known as a “cytokine storm”). Similar to COVID-19, HLH is characterized by aggressive course leading to multi-organ failure.

Main text: The purpose of this review article is to draw attention to the possibility of the complication of HLH in patients with the severe course of COVID-19. Indeed, some of the clinical characteristics observed in the more severe cases of COVID-19 are reminiscent of secondary HLH (which can be triggered by infections, malignancies, rheumatological diseases, or autoimmune/immunodeficiency conditions). The pathogenesis of SARS-CoV-2 infection also suggests that HLH or a similar hyperinflammatory syndrome is the cause of the severe course of the infection.

Conclusion: The pathogenesis and clinical symptoms of severe COVID-19 indicate that an increased inflammatory response corresponding to HLH is occurring. Therefore, patients with severe COVID-19 should be screened for hyperinflammation using standard laboratory tests to identify those for whom immunosuppressive therapy may improve outcomes.

Keywords: Coronavirus, Coronavirus disease 2019, Hemophagocytic lymphohistiocytosis

Background

An acute infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), named the coronavirus disease 2019 (COVID-19), presents an imminent public health threat worldwide. As of the 23rd of June 2020, over 8.8 million cases of COVID-19 have been confirmed worldwide, and the total number of deaths has surpassed 460,000 [1]. Recent reports have summarized the clinical presentation of COVID-19, which commonly presents as fever, cough, dyspnea, and myalgia or fatigue [2–8]. Although the majority of patients with COVID-19 have mild symptoms, some patients (especially those with underlying diseases) are more prone to serious outcomes, including pneumonia, acute respiratory distress syndrome (ARDS), and even death [9, 10]. Current research efforts are focused on identifying the cause of the aggressive course of the disease and the high mortality rates observed with severe COVID-19, as well as developing novel therapies [10].

Some of the clinical characteristics observed in the more severe cases of COVID-19 [6–8] are reminiscent of hemophagocytic lymphohistiocytosis (HLH), a severe, life-threatening inflammatory syndrome associated with intense cytokine release (also known as a “cytokine storm”).
storn") [11]. HLH is characterized by aggressive course leading to multi-organ failure [12]. As HLH can develop in response to viral infections [12], it may be triggered by SARS-CoV-2, which could explain the rapid disease progression observed in some patients.

This review summarizes the pathogenesis and clinical characteristics of COVID-19 that suggests HLH or a similar hyperinflammatory syndrome is the cause of the severe course of the infection. A timely diagnosis of HLH in patients with COVID-19 would offer new therapeutic strategies (e.g., immunosuppression), which in turn, may reduce the significant mortality rates currently associated with this virus.

**Main text**

**HLH: an aberrant immune response to viral infections**

The majority of viral infections acquired by non-immunosuppressed individuals are asymptomatic or result in mild clinical manifestations; however, for those who are immunocompromised or have an immune disorder, viral infections may result in a life-threatening disease, as occurs in the case of HLH (Table 1) [13]. In HLH, aberrant activation of T cells, natural killer (NK) cells, and macrophages causes overproduction of inflammatory cytokines (i.e., the so-called cytokine storm) and hemophagocytosis [13, 14]. This excessive autoimmune response leads to rapidly progressing multi-organ failure [13].

HLH is generally divided into two types: primary or familial HLH (which is observed in pediatric patients) and secondary HLH (sHLH, found also in adults). Primary HLH is caused by genetic defects (e.g., mutations in PRF1 or UNC13D, which are typically involved in the perforin-mediated killing of target cells [11]), while a range of triggers are described for sHLH, including infections, malignancies, rheumatological diseases, or autoimmune/immunodeficiency conditions [13, 14]. Epstein-Barr virus (EBV) and herpes simplex virus (HSV) infections are the most frequent triggers of sHLH, although other viruses (e.g., cytomegalovirus, hepatitis A, parvovirus B19, adenovirus, influenza) and pathogens (e.g., bacteria, fungi, parasites) have also been implicated [13–19]. In cases of primary HLH, several different gene defects can lead to the common phenotype of impaired NK/T cell cytotoxicity [20]. Defects in the function of NK and cytotoxic T cells also lead to excessive inflammation in sHLH, when these cells are activated by an external trigger [20].

**The clinical characteristics of COVID-19 resemble sHLH**

The cardinal features of sHLH are high fever, hepatomegaly, splenomegaly, cytopenia (e.g., anemia, thrombocytopenia, and neutropenia), coagulopathy, central nervous system disturbances, and rapidly progressing multi-organ failure [14, 16–19]. Respiratory symptoms, which commonly present as dyspnea and cough, or ARDS can also occur in patients with sHLH. This phenomenon mostly occurs in cases triggered by respiratory viruses, and the signs of infection may overlap with the symptoms of sHLH [21]. Similarly, the majority of patients with COVID-19 present with high fever (observed in 44% of patients upon presentation, and subsequently, in 64.5–99% patients), cough (45–82%), dyspnea (6.5–63.5%), and myalgia or fatigue (11–70%) [2–8]. Some patients also show liver damage (transaminase activity), lymphocytopenia, and rapidly progressing multi-organ failure [9, 10, 14, 16, 18]. Indeed, a number of the cardinal clinical features of these two conditions are shared, as summarized in Table 2.

In terms of laboratory findings, cytopenia is often observed in sHLH, with thrombocytopenia identified in 80–90% of cases [14, 16, 17, 19]. In addition, almost 60% of patients with HLH have coagulation disorders, while hypofibrinogenemia and raised D-dimer levels are reported in ~40–60% of HLH cases [14, 18, 19]. Furthermore, ~80% of patients have altered liver test results (i.e., increased phosphatase alkaline and transaminase concentrations), and increased serum lactate dehydrogenase (LDH) concentrations resulting from cell destruction are reported in 78–92.8% of patients [14, 16, 18, 19]. Hypertriglyceridemia (associated with lipoprotein lipase inhibition caused by excess tumor necrosis factor-alpha [TNF-α]) is found in ~36–71% of adults with HLH [14, 16, 18, 19]. Increased acute phase

**Table 1** Effects of immune status on the course of viral infections, outcomes, and therapy

| Response to infection | Normal immunity | Immunodeficiency (primary or secondary) | Immune disorder (genetic or acquired) |
|-----------------------|----------------|----------------------------------------|--------------------------------------|
| Course of viral infection | Infection limitation and subsequent elimination | Disseminated, systemic or chronic viral infection | Disseminated or systemic inflammation (i.e., HLH, CRS) |
| Consequences | Recovery | Single or multi-organ failure | Multi-organ failure |
| Potential interventions | Vaccinations | Vaccinations | Immunosuppression |
|                        | Antiviral drugs | Antiviral drugs |                          |
|                        | Intravenous immunoglobulins |                           |                          |

**Abbreviations:** CRS cytokine release syndrome, HLH hemophagocytic lymphohistiocytosis
Table 2: Comparison of severe coronavirus infection and the symptoms of HLH

| Source                                      | Adult HLH | Zhao et al. [19] | Apodaca et al. [16] | Otrock and Eby [18] | Barba et al. [17] | Huang et al. [4] | Chen et al. [2] | Wang et al. [6] | Zhou et al. [8] | Yang et al. | Spiteri et al. [5] |
|---------------------------------------------|-----------|------------------|---------------------|---------------------|------------------|------------------|----------------|----------------|----------------|-------------|---------------------|
| Number of patients (%)                     | 775 (100%)| 171 (100%)       | 64 (100%)           | 73 (100%)           | 41 (100%)        | 99 (100%)        | 138 (100%)     | 191 (100%)     | 52 (100%)       | 31 (100%)   |                     |
| Clinical symptoms belonging to the HLH criteria [22] |           |                  |                     |                     |                  |                  |                |                |                |             |                     |
| Fever                                       |           |                  |                     |                     |                  |                  |                |                |                |             |                     |
| Fever > 37.3 °C                             | 524/546 (96%) | 171/171 (100%)   | 63/64 (94.4%)       | 70/73 (95.9%)       | 59/71 (92%)      | 32/41 (78%)      | 82/99 (83%)   | 136/138 (99%) | 180/191 (94%) ≥ 373 °C | 51/52 (98%) | 20/31 (64.5%) |
| Splenomegaly                                |           |                  |                     |                     |                  |                  |                |                |                |             |                     |
| Splenomegaly > 70%                          | 420/609 (69%) | 146/171 (85.4%)  | 50/64 (78.1%)       | 44/73 (60.3%)       | 27/71 (39%)      | No data          | No data        | No data        | No data        | No data    | No data |
| Hemophagocytosis                            |           |                  |                     |                     |                  |                  |                |                |                |             |                     |
| Hemophagocytosis > 52/68                     | 257/304 (85%) | 152/171 (88.9%)  | 49/64 (76.6%)       | 52/68 (76.5%)       | 57/71 (83%)      | No data          | No data        | No data        | No data        | No data    | No data |
| Cytopenias (affecting at least two lineages) | Yes       | Yes              | 63/64 (98.4%)       | 62/73 (84.9%)       | Yes              | No data          | No data        | No data        | No data        | No data    | No data |
| Anemia (< 9 g/dL)                           | 122/181 (67%) | 98/171 (57.3%)   | 30/64 (46.9%)       | No data             | No data          | No data          | 50/99 (51%)   | No data        | No data        | No data    | No data |
| Neutrophil count of 2.0 – 7.9 × 10^3/mL     |           |                  |                     |                     |                  |                  |                |                |                |             |                     |
| Neutropenia (< 1 × 10^3/mL)                 | 61/144 (42%) | 59/171 (34.5%)   | 9/64 (14%)          | No data             | No data          | Neutrophil count of 2.0–7.9 × 10^3/mL | No data | No data        | No data        | No data    | No data |
| Lymphocytopenia                             | No data   | No data          | 20/64 (31%)         | No data             | No data          | No data          | No data        | No data        | No data        | No data    | No data |
| Leukopenia                                  | 198/285 (69%) | No data         | No data             | 7/71 (10%)          | No data          | No data          | No data        | No data        | No data        | No data    | No data |
| Hypertriglyceridemia > 265 mg/dL            |           |                  |                     |                     |                  |                  |                |                |                |             |                     |
| Hypertriglyceridemia > 265 mg/dL            |           |                  |                     |                     |                  |                  |                |                |                |             |                     |
| Hyperferritinemia (> 500 ng/mL)             |           |                  |                     |                     |                  |                  |                |                |                |             |                     |
| Hyperferritinemia > 1000 ng/mL              | 165/171 (96.5%) | 102/128 (80%)     | 64/64 (100%)        | 73/73 (100%)        | No data          | No data          | No data        | No data        | No data        | No data    | No data |
| Hyperferritinemia > 300 ng/mL               |           |                  |                     |                     |                  |                  |                |                |                |             |                     |
Table 2 Comparison of severe coronavirus infection and the symptoms of HLH (Continued)

| Source | Adult HLH | COVID-19 |
|--------|-----------|----------|
| Ramos et al. [14] | Zhao et al. [19] | Apodaca et al. [16] | Otrock and Eby [18] | Huang et al. [4] | Chen et al. [2] | Wang et al. [6] | Zhou et al. [8] | Yang et al. [7] | Spiteri et al. [5] |
| Elevate sCD25 (soluble IL-2 receptor) | > 2400 IU/mL, 95/120 (79%) | No data | Yes 64/64 (100%) (inclusion criteria) | 24/31 (77.4%) | No data | No data | No data | No data | No data |
| Low or absent NK cell activity | Yes in some patients, but has not yet been standardized | No data | Yes 64/64 (100%) (inclusion criteria) | 4/11 (36.4%) | No data | No data | No data | No data | No data |
| Hypofibrinogenemia (< 150 mg/dL) | 106/171 (62%) | 20/64 (32%) | 24/64 (37.5%) | No data | No data | No data | No data | No data | No data |
| Hepatomegaly | 389/580 (67%) | 70/171 (40.9%) | 46/64 (71.9%) | 13/73 (17.8%) | No data | No data | No data | No data | No data |
| Pulmonary involvement | 61/145 (42%) | No data | 21/64 (32.8%) | No data | ARDS in 44/71 (64%) | ARDS in 12/41 (29%) | ARDS in 17/99 (17%) | ARDS in 27/138 (20%) | ARDS in 59/191 (31%) | No data |
| Peripheral adenopathy | 91/277 (33%) | No data | No data | No data | No data | No data | No data | No data | No data |
| Neurological symptoms | 41/161 (25%) | No data | 10/64 (15.6%) | No data | Confusion or coma in 6/71 (9%) | Headache in 3/38 (8%) | Confusion in 9/99 (9%) | Headache in 9/138 (6.5%) | No data | Headache in 3/52 (6%) | Headache in 6/31 (19%) |
| Multi-organ failure (MOF)/sepsis | ICU admission in ~ 50% of cases | No data | No data | No data | MOF in 11/38 (32%) | ICU care in 13/38 (32%) | ICU care in 23/99 (23%) Sepic shock in 4/99 (4%) | ICU care in 36/138 (26%) | Sepsis in 112/191 (59%) | ICU care in 50/191 (26%) | Sepsis in 1/52 (2%) |
| Renal insufficiency/failure | 9/56 (16%) | No data | 25/64 (39.1%) | 38/73 (52.1%) | No data | 3/41 (7%) | 3/99 (3%) | 5/138 (3.6%) | 28/191 (15%) | 15/52 (29%) | No data |
| Elevated CRP | 80–90% | No data | No data | No data | No data | No data | 63/73 (86%) | No data | No data | No data |
| Elevated serum transaminases | ALT > 40 IU/L, 164/286 (57%) AST > 100 IU/L, 48/115 (42%) | Yes | 47/64 (74%) | 61/73 (83.6%) | No data | AST 15/41 (37%) | ALT 28/99 (28%) AST 35/99 (35%) | No (normal levels) | ALT 59/189 (31%) | 15/52 (29%) | No data |
| Source                          | Adult HLH                                      | COVID-19                                      |
|--------------------------------|-----------------------------------------------|-----------------------------------------------|
|                                | Ramos et al. [14]                             | Huang et al. [4]                              |
|                                | Zhao et al. [19]                              | Chen et al. [2]                               |
|                                | Apodaca et al. [16]                           | Wang et al. [6]                               |
|                                | Otrock and Eby [18]                           | Zhou et al. [8]                               |
|                                | Barba et al. [17]                             | Yang et al. [7]                               |
|                                | Huang et al. [4]                              | Spiteri et al. [5]                            |
| Elevated LDH                  | > 500 IU/L, 190/243 (78%)                     | 29/40 (73%)                                   |
|                                | Yes                                           | 75/99 (76%)                                   |
|                                | No data                                       | 55/138 (40%)                                  |
|                                | 64/69 (92.8%)                                 | 123/184 (67%)                                 |
| Elevated D-dimers              | > 548 mmol/L, 24/49 (49%)                     | No data                                       |
|                                | Yes                                           | No data                                       |
|                                | No data                                       | No data                                       |
|                                | 24/49 (49%)                                   | No data                                       |
| Elevated serum levels of      | Yes                                           | Yes                                           |
| immunological markers (e.g.,  | No data                                       | No data                                       |
| IL-2, IL-7, IL-10, G-CSF,     | No data                                       | No data                                       |
| IP-10, MCP1, MIP1A, TNF-α)    | No data                                       | No data                                       |
| Increased IL-6                 | Yes                                           | Yes                                           |
|                                | No data                                       | No data                                       |
|                                | No data                                       | No data                                       |
|                                | No data                                       | No data                                       |
|                                | No data                                       | No data                                       |

Abbreviations: ALT alanine aminotransferase, ARDS acute respiratory distress syndrome, AST aspartate aminotransferase, CRP C-reactive protein, G-CSF granulocyte-colony stimulating factor, HLH hemophagocytic lymphohistiocytosis, ICU intensive care unit, IFN-γ interferon-γ, IL interleukin, IP-10 interferon-γ-induced protein 10, LDH lactate dehydrogenase, TNF-a tumor necrosis factor-alpha
reactants (i.e., erythrocyte sedimentation rate or C-reactive protein [CRP] concentration) are identified in 62–90% of patients [14, 17]. Moreover, 90–100% of adult sHLH patients show increased ferritin concentrations (due to increased secretion of ferritin by macrophages or hepatocytes) [14, 16, 18, 19]. Finally, high serum concentrations of soluble CD25 (interleukin [IL]-2 receptor-α) occur in 77–79% of adult cases of sHLH [14, 18], although only very high levels of soluble CD25 are specific to HLH [23]. Other markers of macrophage activation (e.g., β2-microglobulin) and cytokines (e.g., interferon [IFN]-γ, TNF-α) are also elevated in HLH [14].

Similar to sHLH, COVID-19 patients present with several laboratory abnormalities, with severe cases showing more prominent abnormalities (i.e., lymphocytopenia, thrombocytopenia, elevated CRP levels) than non-severe cases [24]. Elevated D-dimer, serum ferritin, LDH, and IL-6 levels were also shown throughout the clinical cases [24]. Elevated D-dimer, serum ferritin, LDH, and IL-6 levels were also shown throughout the clinical course of non-surviving patients with SARS-CoV-2 pneumonia compared with survivors [8]. In a series of 1449 hospitalized subjects with COVID-19, baseline and maximum values of prothrombin time, activated partial thromboplastin time, and D-dimer levels were significantly higher in subjects who died than in survivors [24]. Subjects who died had higher fibrinogen concentrations at baseline, but lower minimum values, than survivors [24].

Baseline D-dimer levels and the difference in fibrinogen and platelet levels correlated with an increased risk of death among patients with COVID-19 [24]. Indeed, other observations confirm the relationship between coagulation disorders and prognosis [6, 25, 26].

Coagulation disorders are reported in patients with sHLH, frequently with decreased fibrinogen levels, and can result in severe bleeding complications [27]. Indeed, a low fibrinogen level is one of the main HLH diagnostic criteria [22]. Although this process in HLH is not fully explained, the release of proinflammatory cytokines can cause the release of tissue plasminogen activator and the activation of an alternative fibrinolytic pathway in macrophages [27]. These factors can result in severe consumptive coagulopathy, with elevated fibrinogen degradation and decreased fibrinogen levels. Additionally, liver dysfunction may exacerbate coagulopathy [27]. Therefore, the increase in proinflammatory cytokine release in COVID-19 may lead to analogous coagulation disorders in these patients. Indeed, the abovementioned laboratory abnormalities suggest that a hyper-inflammatory reaction is occurring in patients with severe COVID-19.

**Does SARS-CoV-2 trigger a cytokine storm syndrome?**

Due to the clinical similarities between severe cases of COVID-19 and sHLH, it has been postulated that SARS-CoV-2 may be a trigger for a cytokine storm syndrome, like sHLH [28]. Indeed, previous studies have shown the poor outcomes of patients severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which are caused by SARS-CoV and MERS-CoV, respectively, are associated with high levels of pro-inflammatory cytokines (e.g., IL-1β) in the lower respiratory tract and other tissues [29]. The high expression of IL-1β in these tissues further promotes the expression of other proinflammatory cytokines (e.g., TNF-α and IL-6), resulting in a cytokine storm [30]. For example, activation of NF-κB has been shown to contribute to the inflammation induced after SARS-CoV infection [31]. Similarly, SARS-CoV-2 may trigger sHLH or a related inflammatory syndrome in some patients.

A recent retrospective, multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, reported poor outcomes of patients with elevated ferritin and IL-6, suggesting virally driven hyperinflammation may be associated with mortality [32]. Furthermore, Huang et al. recently reported a cytokine profile resembling sHLH (characterized by increased IL-2, IL-7, granulocyte colony-stimulating factor [G-CSF], IFN-γ-induced protein 10 [IP-10], monocyte chemo-attractant protein 1 [MCP-1], macrophage inflammatory protein [MIP] 1-α, and TNF-α) is associated with the severity of COVID-19 [4]. In particular, IL-6 is thought to contribute to the progression of COVID-19 patients to severe ARDS [33].

A more detailed analysis of the literature has uncovered many similarities between the characteristics observed in severe cases COVID-19 infection and sHLH (as summarized in Table 2). For example, serum ferritin and CRP levels are above the normal range (i.e., in 63–80% and 61–86% of patients, respectively) in patients with severe COVID-19 infection, which is also observed in sHLH [2]. Furthermore, patients with severe COVID-19 infections have been shown to rapidly develop a number of complications, which resemble the multi-organ failure that arises in HLH.

**Severe COVID-19 shows rapid progression similar to HLH**

A characteristic feature of severe COVID-19 is that disease progresses rapidly, and the patient develops multi-organ failure in a short period of time [2]. As is observed in cases of HLH [14, 16, 17, 19], patients with severe COVID-19 show rapid signs of multi-organ damage. For example, among 99 patients diagnosed with SARS-CoV-2 pneumonia, 17% developed ARDS, 8% developed acute respiratory injury, 3% developed acute renal injury, and 4% progressed to septic shock [2]. In addition, among 52 critically ill patients with SARS-CoV-2 pneumonia, 67% had ARDS, 29% had acute renal injury, 23% had cardiac injury, 29% had liver dysfunction, and 2% had pneumothorax [7]. In another retrospective, single-center case series of 138 consecutive hospitalized patients with confirmed SARS-CoV-2 pneumonia, 8.7% developed septic
shock, 19.6% developed ARDS, 16.7% had arrhythmias, and 7.2% had acute cardiac injury [6]. In a retrospective, multi-center cohort including 191 adult inpatients with laboratory-confirmed COVID-19, sepsis was the most frequently observed complication (observed in 59% of cases), followed by respiratory failure (54%), ARDS (31%), heart failure (23%), and then septic shock (20%) [8]. In terms of the times of onset for the various complications arising from COVID-19, sepsis is reported to develop a median of 9 days after illness onset, followed by ARDS (12 days), acute cardiac injury (15 days), acute renal injury (15 days), and then secondary infection (17 days) [8]. As COVID-19 follows a similar pathogenesis to sHLH, early diagnosis and prompt immunosuppression is key, before such multi-organ failure sets in [34].

**Diagnosing HLH in patients with COVID-19**

The diagnosis of sHLH is based on clinical symptoms and results of diagnostic tests. According to the revised HLH-2004 guideline [35], which was recently updated for adult patients [36], the diagnosis is based on five criteria (fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis) and three additional criteria: low/absent NK-cell-activity, hyperferritinemia, and high-soluble IL-2-receptor levels. Other abnormal clinical and laboratory findings consistent with the diagnosis are cerebromeningeal symptoms, lymph node enlargement, jaundice, edema, skin rash, hepatic enzyme abnormalities, hypoproteinemia, hyponatremia, VLDL increase, and HDL decrease. Five of these eight criteria must be fulfilled, unless family history or molecular diagnosis is established for COVID-19 and there is no evidence for specific drug treatment against SARS-CoV-2 in suspected or confirmed cases [36]. To date, no effective clinical management has been established for COVID-19 and there is no evidence for specific drug treatment against SARS-CoV-2 in suspected or confirmed cases [36].

How can an early diagnosis of HLH help in the management of COVID-19?

To date, no effective clinical management has been established for COVID-19 and there is no evidence for specific drug treatment against SARS-CoV-2 in suspected or confirmed cases [36].

For diagnosis and ongoing management of COVID-19, lung imaging (X-ray, computed tomography) and laboratory tests are recommended [41]. Laboratory tests include a throat swab or other respiratory sampling to identify SARS-CoV-2 RNA by PCR; hematologic examination (blood count, lymphocyte subpopulation); tests for common respiratory viruses, mycoplasma, chlamydia, and tuberculosis; liver and renal function tests; myocardial enzyme and myoglobin levels; erythrocyte sedimentation rate; CRP, procalcitonin, lactate, and D-dimer levels; coagulation image; a routine urine test; measurement of inflammatory factors (IL-6, IL-10, TNF-α), complement; and anti-acid staining [41]. These parameters should be constantly monitored in patients with COVID-19. Adding ferritin, fibrinogen, triglycerides, total protein/albumin, and lactate dehydrogenase to laboratory tests would allow early identification of patients with a cytokine storm syndrome like sHLH.

Effective management of COVID-19 would require either prevention (i.e., a vaccine) or, in the case of infection, specific antiviral treatments and inhibitors of generalized inflammation. Moreover, whether treating...
sHLH in the course of COVID-19 improves patients outcomes requires further study. Nonetheless, if a diagnosis of sHLH were to be made in patients with COVID-19, it would be beneficial to control the hyper-inflammatory reaction that leads to multi-organ failure and death. Although HLH management is based on the...
undergo a diagnostic panel of tests (shown in Fig. 1) and patients with worsening or severe COVID-19 should early inclusion of treatment. Therefore, we propose that, again, the effectiveness of this treatment relies on the appropriate treatment.

In addition to the HLH-2004 protocol, an anti-CD19 CAR T cell or blinatumomab treatment (EBV-HLH), some patients may be cured with corticosteroid treatment alone [43]. Furthermore, patients with an infection-associated HLH other than EBV-HLH often enter remission when they are treated with corticosteroids, IVIG, and/or cyclosporine in addition to the treatment for the infectious disease [42]. However, once again, the effectiveness of this treatment relies on the early inclusion of treatment. Therefore, we propose patients with worsening or severe COVID-19 should undergo a diagnostic panel of tests (shown in Fig. 1) and constant monitoring to enable rapid intervention of appropriate treatment.

Controlling the COVID-19 cytokine storm: experimental therapies

In addition to the HLH-2004 protocol, an anti–IL-6 antibody (tocilizumab) was FDA-approved in 2014 for HLH patients aged ≥ 2 years, as it results in rapid resolution of cytokine release syndrome in patients after chimeric antigen receptor (CAR) T cell or blinatumomab treatment [36]. In 2018, a CAR T cell-associated toxicity working group suggested suspected HLH should be managed with anti-IL-6 therapy as well as corticosteroids for those with organ toxicities ≥ grade 3 [36, 44]. Encouragingly, the recently announced COVACTA trial aims to evaluate the safety and efficacy of intravenous tocilizumab in hospitalized adult patients with severe COVID-19 pneumonia (ClinicalTrials.gov Identifier: NCT04320615) [45], and a multicenter, randomized controlled trial of tocilizumab has been approved in patients with COVID-19 pneumonia and elevated IL-6 ≥ 2 in China (Chinese Clinical Trial Registry: ChiCTR2000029765) [46]. In addition, IL-1 blockade with anakinra has shown a significant survival benefit in patients with hyperinflammation [47]. Thus, a clinical study to evaluate the efficacy and safety of anakinra and emapalumab (an anti-IFN-γ antibody that is FDA-approved for adult and pediatric patients with primary HLH) in the treatment of hyperinflammatory syndrome associated with severe cases of COVID-19 is currently underway (ClinicalTrials.gov Identifier: NCT04324021) [48].

Janus kinase (JAK) inhibition is another therapeutic strategy, which could affect both inflammation and cellular viral entry in cases of COVID-19 [49]. Activation of the NF-κB (nuclear factor kappa B) signaling pathway was also shown to contribute to the inflammation induced after SARS-CoV-1 infection [31]; therefore, NF-κB inhibitors may be promising for the treatment of severe COVID-19. Thus, there are a number of exciting new therapies in the pipeline to combat severe cases of COVID-19.

Conclusion

SARS-CoV-2 is also a novel human pathogen that may interact with host antiviral defense in a unique manner. Severe cases of COVID-19 share a number of clinical characteristics with HLH. Without early diagnosis and prompt appropriate treatment, the mortality rate of HLH is very high [13]. Therefore, it is recommended all patients with severe COVID-19 should be screened for hyperinflammation using standard laboratory tests and the HScores [35] to identify the subgroups of patients for whom immunosuppressive therapy may improve outcomes. We acknowledge that a different set of criteria may be required to diagnose patients with COVID-19-associated HLH [39]. Management by a multidisciplinary team of experts (including hemato-oncologists, immunologists, rheumatologists, and intensivists) will be required to provide patients with access to such a full range of treatment options.

Abbreviations

ALT: Alanine aminotransferase; AS1T: Aspartate aminotransferase; ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; C5aR: Cytokine release syndrome; G-CS: Granulocyte-colony stimulating factor; IFN: Hemophagocytic lymphohistiocytosis; IL: Interferon-γ; IFN-γ: Interferon-γ-induced protein 10; JAK: Janus kinase; LDH: Lactate dehydrogenase; MABS: Macrophage activation syndrome; MERS: Middle East respiratory syndrome; MIP: Macrophage inflammatory protein; NK: Natural killer; NF-κB: Nuclear factor kappa B; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; SARS: Severe acute respiratory syndrome; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SHLH: Secondary hemophagocytic lymphohistiocytosis; SOFA: Sequential [Sepsis-Related] Organ Failure Assessment Score; TNF-α: Tumor necrosis factor-alpha

Acknowledgements

Not applicable

Authors’ contributions

All of the authors contributed substantially to the preparation of this review and met the authorship criteria according to the International Committee of Medical Journal Editors (ICMJE) guidelines. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by the Polish National Science Center (grant no. UMO-2016/21/B/NZ6/02279) and the Medical University of Lublin (grants no. DS460 and DS461).
References

1. Coronavirus disease (COVID-19) Pandemic. [https://www.who.int/emergencies/diseases/novel-coronavirus-2019]. Accessed 23 June 2020.

2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10233):507–13.

3. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He JX, Liu S, Shan H, Lei CL, DSC H, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–1720. https://doi.org/10.1056/NEJMoa2002302.

4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Yang X, Gu X, Xu J, Gao R, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. JAMA. 2020; 323(11):106–12.

5. Spiteri G, Fielding J, Berkovski M, Campese C, Enouf V, Gaymard A, Bella A, Sognamiglio P, Sierra Moros MJ, et al. First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020. Euro Surveill. 2020;25(9):2000178. https://doi.org/10.2807/1560-7917.ES.2020.25.9.2000178.

6. Wang D, Hu B, Hu C, Zhu F, Liu X, Xiong Y, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020; 323(11):1061–9.

7. Yang X, Yu Y, Xia J, Shu H, Xia JA, Liu H, Wu Y, Zhang L, Yu Z, Fang M et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475–81. https://doi.org/10.1016/S2213-2690(20)30379-5.

8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.

9. Fang S-Y, Yuen K-S, Ye Z-W, Chan P-C, Jin D-Y. A tug-of-war between severe acute respiratory syndrome coronavirus 2 and host antiviral defence: lessons from other pathogenic viruses. Emerging Microbes Infect. 2020;9(1):558–70.

10. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020;7(11).

11. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annu Rev Med. 2012;63:33–46.

12. Marsh RA. Epstein–Barr virus and hemophagocytic lymphohistiocytosis. Front Immunol. 2018;8:1902.

13. Dropulic LK, Cohen JI. Severe viral infections and primary immunodeficiencies. Clin Infect Dis. 2011;53(9):897–909.

14. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X, Adult haemophagocytic syndrome. Lancet. 2014;383(9922):1503–16.

15. Han X-C, Ye Q, Zhang W-Y, Tang Y-M, Xu X-J, Zhang T. Cytokine profiles as novel diagnostic markers of Epstein-Barr virus–associated hemophagocytic lymphohistiocytosis in children. J Crit Care. 2017;39:72–7.

16. Apodaca E, Rodriguez-Rodriguez S, Tuna-Aguilar EJ, Demichelis-Gomez R. Prognostic factors and outcomes in adults with secondary hemophagocytic lymphohistiocytosis: a single-center experience. Clin Lymphoma Myeloma Leuk. 2018;18(10):e373–80.

17. Barba T, Maucort-Boulch D, Iwaz J, Bohe J, Ninet J, Hot A, Lega JC, Guerin C, Argaud L, Broussole C, et al. Hemophagocytic lymphohistiocytosis in intensive care unit: a 71-case strobé-compliant retrospective study. Medicine (Baltimore). 2015;94(51):e2318.

18. Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. Ann J Hematol. 2015;90(3):220–4.

19. Zhao Y, Lu D, Ma S, Li L, Zhu J, Zhou, Zheng Y, Yang X, Zhu L, Zhu M, et al. Risk factors of early death in adult patients with secondary hemophagocytic lymphohistiocytosis: a single-institution study of 171 Chinese patients. Hematology. 2019;24(1):69–12.

20. Usmani GN, Woda BA. Newburger PE. Advances in understanding the pathogenesis of HH. Br J Haematol. 2013;161(5):609–22.

21. Seguin A, Galicier L, Bouboulou D, Lemiale V, Azoulay E. Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. Chest. 2016;149(5):1294–301.

22. Henter J, Home A, Aricò M, Egeler RM, Filipovic AH, Imachi S, Ladhisch S, McClain K, Webb D, Winiarski I, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124–31.

23. Hayden A, Lin M, Park S, Pudek M, Schneider M, Jordan MB, Mattman A, Chen LHC. Soluble interleukin-2 receptor is a sensitive diagnostic test in adult HH. Blood Advances. 2017;1(26):2529–34. https://doi.org/10.1182/bloodadvances.2017009910-0110.

24. Li Q, Cao Y, Chen L, Wu D, Yu J, Wang H, He W, Chen L, Dong F, Chen W, et al. Hematological features of persons with COVID-19: Leukemia. 2020.

25. Rodelo JR, De la Rosa G, Valencia ML, Ospina S, Arango CM, Gomez CI, Garcia A, Nuñez E, Jaimey FA. D-dimer is a significant prognostic factor in patients with suspected infection and sepsis. Am J Emerg Med. 2012;30(8):1991–9.

26. 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(4):844–7.

27. Valade S, Mariotte E, Azoulay E. Coagulation disorders in haemophagocytic lymphohistiocytosis/macrophage activation syndrome. Crit Care Clin. 2020; 36(2):415–26.

28. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.

29. He L, Ding Y, Zhang Q, Che X, He Y, Shen H, Wang H, Li Z, Zhao L, Geng J, et al. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. J Pathol. 2006;201(3):288–97.

30. Nieto-Torres JL, DeDiego ML, Verdín-Báguena C, Jiménez-Guareño JM, Regla-Nava JA, Fernandez-Delgado R, Castaño-Rodríguez C, Alcaraz A, Torres J, Aguillera VM, et al. Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. PLoS Pathog. 2014;10(3):e1004077.

31. DeDiego ML, Nieto-Torres JL, Regla-Nava JA, Jiménez-Guareño JM, Fernandez-Delgado R, Fett C, Castaño-Rodríguez C, Perlman S, Enjuanes L. Inhibition of NF-kB-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increases survival. J Virol. 2014;88(2):913–24.

32. 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 Medicine. 2020;46(5):846–8. https://doi.org/10.1007/s00134-020-06091-x.

33. Chen C, Zhang XR, Ju ZY, He WF. Advances in the research of cytokine storm mechanism induced by coronavirus disease 2019 and the corresponding immunotherapies. Zhonghua Shao Shang Za Zhi. 2020;36(0):E005.

34. Ramachandran S, Zaidi F, Aggarwal A, Gera R. Recent advances in diagnostic and therapeutic guidelines for primary and secondary Hemophagocytic lymphohistiocytosis. Blood Cell Mol Dis. 2017;64:53–57. https://doi.org/10.1016/j.bcmd.2016.10.023.

35. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, Coppel P, Hejblum G. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2020;72(5):2613–20.
36. La Rosée P, Horne A, Hines M, von Bahr GT, Machowicz R, Berliner N, Birndt S, Gil-Herrera J, Girschikofsky M, Jordan MB, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019;133(23):2465–77.

37. Hscore [http://saintantoine.aphp.fr/score/]. Accessed 23 June 2020.

38. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Coopersmith CM, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.

39. Mehta P, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in hemophagocytic lymphohistiocytosis or macrophage activation syndrome. Lancet Rheumatol. 2020;2(6):e358–67.

40. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, Kochanek M, Böll B, von Bergwelt-Baldon MS. Cytokine release syndrome. J ImmunoTherapy Cancer. 2018;6(1):56.

41. Jin Y-H, Cai L, Cheng Z-S, Cheng H, Deng T, Fan Y-P, Fang C, Huang D, Huang L-Q, Huang Q, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Military Med Res. 2020;7(1):4.

42. Morimoto A, Nakazawa Y, Ishii E. Hemophagocytic lymphohistiocytosis: pathogenesis, diagnosis, and management. Pediatr Int. 2016;58(9):817–25.

43. Shiraishi A, Ohga S, Doi T, Ishimura M, Takimoto T, Takada H, Miyamoto T, Abe Y, Haru T. Treatment choice of immunotherapy or further chemotherapy for Epstein–Barr virus-associated hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2012;59(2):265–70.

44. Neelapu SS, Tummala S, Keating A, Wierda W, Gutierrez C, Locke FL, Komanduri KV, Lin Y, Jain N, Daver N, et al. Chimeric antigen receptor T-cell therapy — assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47–62.

45. A study to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia (COVACTA). ClinicalTrials.gov Identifier: NCT04320615 [https://clinicaltrials.gov/ct2/show/NCT04320615]. Accessed 23 June 2020.

46. A multicenter, randomized controlled trial of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). Chinese Clinical Trial Registry: ChiCTR2000029765 [http://www.chictr.org.cn/showprojen.aspx?proj=49409]. Accessed 23 June 2020.

47. Shakoory B, Carcillo J, Chatham W, Amdur R, Zhao H, Dinarello C, Cron R, Opal S. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome. Crit Care Med. 2015;44(1).

48. Efficacy and safety of emapalumab and anakinra in reducing hyperinflammation and respiratory distress in patients with COVID-19 infection. ClinicalTrials.gov Identifier: NCT04324021 [https://clinicaltrials.gov/ct2/show/NCT04324021]. Accessed 23 June 2020.

49. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Stebbing J. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395(10233):e30–1.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.