# Neonatal COVID and Familial Hemophagocytic Lymphohistiocytosis

***To the Editors:***

Children with inflammatory syndromes often present with vague and nonspecific symptomatology that pose diagnostic and management challenges to emergency care physicians.[1–3] The initial hours of management is critical because it determines the clinical course and eventual clinical outcome. We recently managed the case of an asymptomatic neonate who recovered from COVID-19 infection but developed hemophagocytic lymphohistiocytosis (HLH) a few weeks later. Mutations of UNC13D genes were detected in the patient and his father. His clinical course is complicated with human herpesvirus 6 and *Escherichia coli* K1 meningitis. Multidisciplinary team approach is adopted in the management of this patient. The definitions of many of the hyperinflammatory syndromes and acronyms are poorly defined and overlapping.[4] Worse still, many novel and confusing syndromes are coined and loosely linked to coronavirus infection (eg, pediatric multisystem inflammatory syndrome (PMIS), multisystem inflammatory syndrome in children (MIS-C), or pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; PIMS-TS); COVID toe syndrome; COVID skin syndromes).[5,6] The current case leads us to consider 2 fundamental concepts. First, it is debatable if infection with SARS-CoV-2 could lead to hyperinflammatory syndromes such as cytokine release syndrome (CRS), cytokine storm syndrome (CSS), and many confusing abbreviations, notoriously PMIS, MIS-C, or PIMS-TS.[6,7] Since SARS in 2003, it has been generally agreeable by experts that some cases of coronavirus and respiratory viral infections are associated with hyerpinflammation.[8] Hence, management of severe cytokine CRS and CSS would include anti-inflammatory medications such as corticosteroids and immunomodulating agents.[8] The second controversy is whether coronavirus infection can trigger onset of cytopenia and hemophagocytosis associated with familial HLH and UNC13D mutations.[9] Cytopenia, lymphopenia, and HLH associations have been reported with coronavirus infection in adults.[7,10–12] However, there has been no such association of "neonatal

**TABLE 1.** Diagnostic Criteria and Clinical Features of Different Inflammatory Syndromes

| | PMIS, MIS-C, or PIMS-TS[6] | CRS and CSS[13–15] | SIRS[16] | HLH[17,18] | MAS[18–20] |
|---|---|---|---|---|---|
| Diagnostic criteria | • Persistent fever >38.5°C inflammation, >1 organ dysfunction with additional clinical features<br>• ↑Ferritin, IL-6, and CRP if CSS[21]<br>• ↑CRP | • Fever<br>• CRS is SIRS triggered by infections and certain drugs.<br>• When occurring as a result of a therapy, CRS symptoms may be delayed until days or weeks after treatment. Immediate-onset (fulminant) CRS appears to be a CSS.<br>• CSS is due to deranged innate immune system.<br>• CSS is a severe episode of CRS or a component of MAS.<br>• ↑Ferritin, D-dimer, aspartate aminotransferase, lactate dehydrogenase, CRP, neutrophils, procalcitonin and creatinine, IL-6, and IFN-γ<br>• Ferritin, IL-6, and CRP if COVID-19 (23) | ≥2 of 4 criteria, one must be abnormal temperature or leukocyte count<br>• Core temperature >38°C (100.4°F) or <36°C (96.9°F)<br>• Heart rate >90 beats/min<br>• Respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg<br>• WBC count >12,000/mm$^3$, <4000/mm$^3$, or >10% bands/ immature forms | 1. Molecular diagnosis consistent with HLH-associated gene mutations: PRF1, UNC13D, or STX11.<br>OR<br>2. 5 of the 8 criteria below:<br>• Fever (>38°C)<br>• Splenomegaly<br>• Decreased blood cell counts affecting at least 2 of 3 lineages in the peripheral blood:<br>- Hemoglobin <9 g/ 100 mL (in infants aged <4 wk: hemoglobin <10 g/ 100 mL) (anemia)<br>- Platelets <100 × 109/L (thrombocytopenia)<br>- Neutrophils <1 × 109/L (neutropenia)<br>• High blood levels of triglycerides (fasting, ≥265 mg/100 mL) and/or decreased amounts of fibrinogen in the blood (≤150 mg/100 mL)<br>• Ferritin ≥500 ng/mL | A severe, potentially life-threatening, complication of several chronic rheumatic diseases of childhood such as SoJIA, SLE, Kawasaki disease, and adult-onset Still disease.<br>Pathophysiologically very similar to reactive (secondary) HLH<br>A febrile patient with:<br>Ferritin >684 ng/mL and any 2 of the following:<br>Hemoglobin <90 g/L (in infants aged <4 wk: <100 g/L)<br>Platelets <100 × 109/L<br>Neutrophils <1.0 × 109/L<br>Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL)<br>Fibrinogen ≤1.5 g/L<br>Other specific markers of macrophage activation (eg, soluble CD163) and lymphocyte activation (eg, soluble IL-2 receptor)<br>NK cell function analysis may show depressed NK function, or flow cytometry may show a depressed NK cell population.[22] |

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**TABLE 1.** *(Continued)*

| | PMIS, MIS-C, or PIMS-TS[6] | CRS and CSS[13–15] | SIRS[16] | HLH[17,18] | MAS[18–20] |
|---|---|---|---|---|---|
| | | | | • Hemophagocytosis in the bone marrow, spleen, or lymph nodes<br>• Low or absent natural killer cell activity<br>• Soluble CD25 (soluble IL-2 receptor) >2400 U/mL | IL-6<br>IFN-γ<br>GM-CSF<br>↓ Erythrocyte sedimentation rate |
| Hematological | Neutrophilia<br>Lymphopenia | Neutrophilia<br>Lymphopenia | Leukocyte count elevated or depressed for age or >10% immature neutrophils<br>Elevated IL-6 | • Splenomegaly<br>• Cytopenia (≥2 of 3 lineages) as above<br>• Hemophagocytosis in bone marrow or spleen or lymph nodes<br>• Fibrinogen ≤1.5 g/L | • Hyperferritinemia, hepatopathy, coagulopathy, thrombocytopenia, hypertriglyceridemia, and bone marrow hemophagocytosis |
| Respiratory | Organ dysfunction<br>Oxygen requirement<br>Cough<br>Sore throat | Hypoxia, ARDS | • RR > 2 SD above normal for age<br>• Mechanical ventilation not related to underlying disease/ general anesthesia | ARDS | ARDS |
| Cardiovascular | Organ dysfunction<br>Hypotension | Cardiomyopathy and shock | • Tachycardic, mean HR >2 SD above normal age<br>• Age <1 y: bradycardia (mean HR <10th percentile) | Shock | Shock |
| Hepatic/ gastrointestinal | Organ dysfunction<br>Abdominal pain<br>Diarrhea<br>Vomiting | Acute hepatic injury | - Acute hepatic injury if shock | Fasting triglycerides ≥3 mmol/L | • Hepatosplenomegaly,<br>• Hepatic dysfunction |
| Other | Exclusion of microbial cause<br>± SARS-CoV-2<br>• Conjunctivitis<br>Lymphadenopathy<br>Neck swelling<br>Mucus membrane changes<br>Rash<br>Swollen hands and feet<br>Encephalopathy | Infectious and noninfectious etiologies (eg, CAR-T)<br>• Fatigue, headache, rash, or muscle or joint pain<br>• Hypotension, tachycardia, capillary leakage, edema, MODS, death<br>• Encephalopathy | | No evidence of malignancy | Lymphadenopathy |

ARDS indicates acute respiratory distress syndrome; CAR-T, chimeric antigen receptor T-cell therapy; COVID-19, coronavirus disease; CRP, C-reactive protein; CRS, cytokine release syndrome; CSS, cytokine storm syndrome; HLH, hemophagocytic lymphohistiocytosis; IL-6, interleukin 6; MAS, macrophage activation syndrome; MICS-C, multisystem inflammatory syndrome in children; PIMS, pediatric multisystem inflammatory syndrome; PIMS-TS, paediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2; RR, respiratory rate; SIRS, systemic inflammatory response syndrome; SoJIA, systemic-onset juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; SD, standard deviation; WBC, white blood cell.

COVID" and "familial HLH" reported for "COVID hemophagocytosis syndrome" or "COVID HLH syndrome."

To aid understanding and diagnosis, a table of the latest definition for these inflammatory syndromes is compiled (Table 1). Cytokine release syndrome refers to a form of systemic inflammatory response syndrome (SIRS) that can be triggered by infections or certain drugs. Severe and acute CRS is termed CSS (Table 1).[23,24] Hemophagocytic lymphohistiocytosis is one of the CSSs of severe hyperinflammation caused by uncontrolled proliferation of activated lymphocytes, macrophages, and secretion of inflammatory cytokines.[17,18] Macrophage-activation syndrome (MAS) is a severe complication of chronic rheumatic diseases of childhood pathophysiologically similar to reactive (secondary) HLH.[19] Unlike MIS-C, CRS, CSS, and SIRS, HLH and MAS are associated with cytopenia.

For emergency physicians, the general treatment strategy for these syndromes of inflammation with or without cytokine storm involves supportive care to maintain critical organ function, control of the underlying

disease, and elimination of triggers for abnormal immune system activation. Multidisciplinary approach is adopted to provide targeted immunomodulation or nonspecific immunosuppression to limit the collateral damage of the activated immune system.[13] Correct therapeutics of immunomodulating agents and avoidance of immune triggering drugs are important in these inflammatory syndromes.[17]

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