***CDI COVID-19 Survival Toolkit: Unraveling Cytokine Storms with Secondary Hemophagocytic Lymphohistiocytosis***

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The term “cytokine storm” describes a process that begins when the immune system overreacts and triggers the inflammatory response, which spins out of control and can ultimately lead to multi-organ failure and death.

***What are cytokines?***

Cytokines are small proteins that act to initiate immune responses while also stimulating the cells to move towards sites of inflammation, infection and trauma. Cytokines help to fight off infections and can act to ward off cancer cells and therefore, are designed to work for us, not against us.

***The cytokine storm***

Known as “cytokine release syndrome” (CRS), a cytokine storm is a toxic process that occurs when cytokines act beyond what they are meant for. To put it simply, it’s an over-reaction of the immune response that doesn’t turn off when the threat is over.

There are many triggers for the initiation of a cytokine storm such as infections (both viral and bacterial), rheumatic diseases such as lupus and certain types of blood cancers.

Most importantly, cytokine storms can develop in many conditions such as systemic inflammatory response syndrome (SIRS), sepsis, secondary hemophagoctyic lymphohistiocytosis (sHLH), macrophage activation syndrome (MAS) and tumor lysis syndrome. *The key is appropriate identification of the condition the storm is causing.*

***COVID-19 and secondary hemophagocytic lymphohistiocytosis (sHLH)***

An article from *The Lancet* published on March 16, 2020, “[COVID-19: Consider Cytokine Storm Syndrome and Immunosuppression](https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736%2820%2930628-0.pdf)” says the following: “Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome.” This article brings sHLH to the forefront stating that it is an often an under-diagnosed condition that could very well be playing a major role in the mortality rate for COVID-19 patients.

***sHLH***

There are actually two types of hemophagocytic lymphohistiocytosis, one that affects the pediatric population (HLH) and one that affects the adult population (sHLH).

In [the April 1, 2020, episode of the *ACDIS Podcast: Talking CDI*](https://acdis.org/acdis-podcast/sepsis-cytokine-release-syndrome-and-covid-19), Cesar Limjoco, MD, described sHLH as “difficult to diagnose and the diagnosis is often missed as it can mimic SIRS or Sepsis.” Dr. Limjoco went on to say that it is an unfamiliar diagnosis to most physicians and that many physicians revert to familiar terms such as viral sepsis or septic shock to describe what is going on with the patient.

The article “[Hemophagocytic Lymphohistiocytosis](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4816886/)” also says that “sHLH is seen more in viral infections (e.g., SARS-CoV-2 causing COVID-19) than bacterial infections (e.g., mycobacteria).”

***Clinical presentation of sHLH***

There are specific characteristics of sHLH that make it distinct from other diagnoses. A [research study done in 2004 recommended by the Histiocyte Society](https://emcrit.org/pulmcrit/sepsis-hlh-overlap-syndrome-shlhos/) concluded that five out of eight of the below symptoms are diagnostic for sHLH:

* Fever
* Splenomegaly
* Cytopenia in at least two cell types
* Hypertriglyceridemia or hypofibrinogenemia
* Hemophagocytosis (via biopsy)
* Ferritin >500 mcg/L
* Low/absent NK cell activity
* Soluble CD25 elevation

Other manifestations can include shock, disseminated intravascular coagulation, and multi-organ failure. Acute respiratory distress syndrome is documented as occurring in approximately 50% of patients.

***Treatment of sHLH***

Per the Histiocyte Society, the first treatment protocol for patients with sHLH included a combination of chemotherapy, immunotherapy and steroids, as well as antibiotics and antiviral drugs. Treatment for the underlying cause and associated manifestations should also be implemented but will vary based on the clinical presentation of the patient and physician’s preference.

***Conclusion***

The latest Sepsis-3 definition is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection with a mean mortality rate of 32.5% for non-intubated patients and 48% for intubated patients. sHLH is defined as is a life-threatening hyperinflammatory syndrome that can occur in patients with severe infections, malignancy or autoimmune diseases with a mean mortality rate of roughly 40%-50% for critical patients with multi-organ failure.

The similarities are undeniable and further exploration is warranted. Certainly, we do not want to bombard our physicians with information and/or questions during this time of crisis. However, once the current crisis settles down, however, CDI specialists can begin to have discussions with providers so that the appropriate diagnoses can be investigated which could ultimately serve to save patients through appropriate treatment regimens.

***References***

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