



Taming the Cytokine Storm During COVID-19

NEW DEVICES FOR TREATMENT

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A cytokine storm, also called cytokine storm syndrome (CSS) or hypercytokinemia, occurs when the human immune system causes uncontrolled release of cytokines, leading to a cytokine storm. Cytokines are proteins released when pathogens invade the body, but sometimes the immune system does not turn itself off and leads to the patient's rapid decline.

A CSS could be triggered by variety of conditions:

- Blood cancers such as leukemia and lymphoma
- Graft-versus-host disease

- Macrophage activation syndrome (MAS) often part of autoimmune disorders such as Lupus, juvenile or rheumatoid arthritis or Still's disease
- Hemophagocytic Lymphohistiocytosis
- Sepsis
- Viral infections such as COVID-19, Epstein-Barr virus and other herpes viruses

There are two types of Hemophagocytic Lymphohistiocytosis (HLH) that could trigger a CSS:

- Primary - inherited disease affecting infants and children (HLH)

- Secondary - usually caused by viral agents (such as SARS-CoV-2, Epstein-Barr virus, etc.) or cancer affecting the adult population (sHLH)

The International Histiocyte Society is suggesting five of the following clinical criteria must be met when diagnosing HLH:

- 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 and multi-organ failures such as acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulopathy (DIC).

As we know, some of the above criteria could also be seen in patients with sepsis, SIRS, MODS and MAS. However, the therapies for those conditions as well as the mortality outcomes are different.

Chemotherapy, immunotherapy, steroids, antibiotics, antiviral drugs or stem cell transplants are used for HLH, antibiotics and supportive treatment for sepsis, SIRS, and MODS and immune suppression drugs are utilized for MAS.

The drug tocilizumab (Actemra) is showing promising results at blocking a cytokine called "interleukin-6 (IL-6)" and lowering the fatal outcomes related to cytokine storm due to high IL-6 levels. Another drug, Kineret, is proving to be successful at blocking another cytokine called

"COVID IS – MAYBE – A RELATIVELY UNIQUE CYTOKINE STORM. IT SEEMS TO HAPPEN QUICKLY WITH THIS VIRUS." – RANDY CRON

interleukin-1 (IL-1). But researchers are still investigating drugs that could reduce the cytokine inflammation at its origin and not just block a single cytokine. According to a study published in June 2020 in the Journal of Science Immunology, the cancer drug acalabrutinib (Calquence), a selective bruton tyrosine kinase inhibitor, rapidly lowers

the measures of inflammation (C-reactive protein and IL-6) as well as lymphopenia in tandem with improved oxygenation.

In addition, in April 2020 the FDA has emergently approved two new devices for treatment of cytokine storm in COVID-19 patients (18 years of age or older) by extracorporeal blood purification through special membranes with enhanced

adsorptive profiles – CytoSorb and Oxiris (oXiris). CytoSorb has been used in Europe since 2013 for blood purification. The device filters out molecules with the approximate size of the cytokines and "one cartridge could purify an entire body's blood volume roughly 70 times" in 24 hrs. Even though the device could remove some proteins that the body needs, the benefit of timely removal of the high levels of cytokine proteins leading to the CSS is more important. CytoSorb is used in current trials together with tocilizumab for synergistically reducing the circulating inflammatory mediators of hypercytokinemia.

The article "COVID-19 and Secondary Hemophagocytic Lymphohistiocytosis (sHLH) versus Sepsis" compares sHLH and sepsis. According to Dr. Limjoco, physicians could use "these terms synonymously" and the sHLH is very often undiagnosed. Since Sepsis, SIRS, and sHLH could present with common clinical criteria, the physician could document sepsis or SIRS with shock instead of sHLH shock. But if there is a bacterial infection superimposed on a viral one (for example bacterial pneumonia) leading to sepsis, then both conditions could co-exist.

Appropriate queries to capture the primary and secondary infection(s) based on clinical criteria with the present on admission indicators could be appropriate and would help with better reflecting the patient condition and treatment modality.

Resources

acdis.org/articles/ask-acdis-covid-19-and-cytokine-storms

acdis.org/resources/cdi-covid-19-survival-toolkit?utm_source=editorial&utm_medium=ACDIS&utm_campaign=MayJuneJour

aferetica.com/wp-content/uploads/2020/03/Aggiornamento_Cytosorb_Coronavirus_ENG.pdf

frontiersin.org/articles/10.3389/fped.2020.00413/full

hopkinsmedicine.org/health/conditions-and-diseases/hemophagocytic-lymphohistiocytosis

icd10monitor.com/covid-19-and-secondary-hemophagocytic-lymphohistiocytosis-shlh-versus-sepsis

immunology.sciencemag.org/content/5/48/eabd0110

m2pharma.com/news/therapy-areas/devices/article.php?id=85207

nytimes.com/2020/06/11/health/coronavirus-cytokine-storm.html

pubmed.ncbi.nlm.nih.gov/19325510/

wikipedia.org/wiki/Cytokine_storm

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