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# Understanding cytokines for more accurate COVID-19 reporting

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One of the most frustrating aspects of the novel coronavirus (COVID-19) pandemic is dealing with the unknown. Our understanding of COVID-19 and its sequelae/manifestations is continually evolving. There is one "manifestation" of COVID-19 that is of interest for experimental treatment: cytokine release, or storm. First, let's define cytokines. During an infection, the immune system increases the release of molecules called cytokines. These molecules circulate in the bloodstream like messengers calling upon immune cells to fight the offender (whether an infectious process or a misguided attack on the body).

In some patients, for largely inexplicable reasons, this release continues even after the invading pathogen or body system is being destroyed by antibiotics, antivirals, and/or our immune system. This uncontrolled response causes collateral damage to tissues, especially lung tissue.

Several studies that analyzed cytokines (published prior to this pandemic) have described a "cytokine storm" as a release of specific types of cytokines: interleukins (IL) to be exact. These include IL-1, IL-6, IL-12, and IL-18, along with tumor necrosis factor (TNF) alpha and other inflammatory mediators. The sustained, excessive cytokine release—or storm—is found in a variety of infectious diseases, including influenza, COVID-19, Ebola, and sepsis, and is often a cause of (or contributor to) mortality.

Once cytokines have started this hyperactive response to a perceived threat, what happens next? The cytokines and TNF directly attack tissues and organs. When a cytokine storm due to an infectious process occurs, the body receives a double insult: the direct attack of the infectious agent, as well as an immune system attack. This attack presents as a systemic inflammatory response syndrome (SIRS) with resultant end-organ damage.

**ICD-10-CM reporting**

In considering COVID-19, what documentation options are available to represent the cytokine release syndrome/storm? Per *Coding Clinic,* First Quarter 2020, no unique code assignment is available for cytokine release syndrome. Also note that cytokine storm is not listed in the ICD-10-CM Alphabetic Index. We can be hopeful that a unique code for this condition will be available one day. In the interim, however, what are the best options for documentation and reporting?

- Codes for the resultant manifestations, such as acute respiratory distress syndrome, tachycardia, and neutropenia may be reported according to the *ICD-10-CM Official Coding Guidelines for COVID-19* since there is not a unique code currently available for the syndrome.
- SIRS cannot be coded since COVID-19 is an infectious condition. It would not be appropriate to query for or code SIRS due to non-infectious condition.
- A code for sepsis may be assigned when documented by a provider. Please refer to your facility guidelines for sepsis criteria.
- A code for secondary hemophagocytic lymphohistiocytosis (HLH) may be assigned when documented by a provider. HLH is a life-threatening syndrome of excessive immune activation. It can be either a primary HLH due to a genetic mutation or secondary (such as due to an infectious cause). Note there is only one ICD-10-CM code for HLH (D76.1). Viral infection has been reported as a common trigger in adults. Secondary HLH criteria is similar to SIRS with additional findings of:
    - Cytopenia
    - Hepatosplenomegaly
    - High serum ferritin
    - Neurologic symptoms

- Pulmonary involvement

When reviewing recent COVID-19 cases, it appears that secondary HLH is a better fit than sepsis. However, because the diagnostic waters are quite muddy, it is best to discuss this with an infectious disease physician in order to differentiate between SIRS with sepsis versus secondary HLH.
Treatment of COVID-19 patients is directed toward:

- Anti-viral therapy such as Remdesivir
- Immune response modifiers, including IL-6 inhibiting medications such as Sarilumab and Tocilizumab (normally used in treatment of auto-immune diseases)
- Organ system support

**Conclusion**
It will be interesting to see which treatments are effective in combating not only the virus directly, but in reducing the cytokine effects without rendering the immune system helpless. Coders and CDI specialists are encouraged to discuss the various diagnosis options with providers so that documentation fully represents the effects of the cytokine release.

In this way, we can ensure an accurate reflection of the severity of illness and risk of mortality of hospitalized COVID-19 patients.

***Editor's note:*** *Manchenton is a senior inpatient consultant/quality services lead at 3M Health Information Systems based in Salt Lake City, Utah.*