CONNECTICUT MEDICAL ASSISTANCE PROGRAM DEPARTMENT OF SOCIAL SERVICES & HEALTH INFORMATION DESIGNS

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Cytokines are a large group of small intercellular proteins that are produced and secreted by cells in the human body to facilitate messaging and communication between cells. Cytokines are capable of autocrine, paracrine and/or endocrine action which can initiate different responses such as mediation of cell differentiation, cell migration, and cell growth or death. Many cytokines are pleiotropic, having multiple functions, depending on their target cell or what other cells are nearby at the time of their release. Because of the complex nature of cytokines, nomenclature for this diverse group of molecules has been challenging.[1] Cytokines were once classified and named based on their cells of origin. For example, lymphocyte cytokines were once called lymphokines and monocyte cytokines were called monokines. But in 1979, Aarden, et al wrote a 'letter-to-the-editor' of the Journal of Immunology[2] suggesting a more streamlined approach by using interleukin (IL) nomenclature with a corresponding numerical assignment. While certain cytokine classes maintained their descriptive names such as the tumor necrosis factors and colony stimulating factors, many cytokines now follow the IL nomenclature suggested by Aarden.[3] See table 1 for cytokine classes and examples.

Cytokines are an integral part of host immunity which can be considered a two-part system: innate and adaptive. Innate immunity provides immediate defense against host intrusion or injury and includes many cells such as dendritic cells (DCs), neutrophils, natural killer (NK) cells, lymphocytes, monocytes, eosinophils, mast cells and macrophages.[4] In order to help facilitate host immune response against intrusions such as infection or trauma, these front line cells utilize cytokines and chemokines to communicate with other innate immunity cells as well as adaptive immunity cells. Adaptive immunity is more deliberate.[4] B and T cells are the foundation of the adaptive system and work to clear infection or intrusion by targeted mechanisms. These cells are also the source of antibody production and memory cells which are a necessary part of the immune system in order to protect against infections. (Figure 1).

The release of proinflammatory cytokines results in inflammation and a cascade of events that calls together both innate and adaptive immunity to clear the danger. If the immune system works as it should and the stimulus is cleared, there will be a negative feedback cascade and proinflammatory cytokines and downstream immune cells are dampened. The balance of pro and anti-inflammatory cytokines is key to immune homeostasis, and if one part of the cascade is dysregulated, it can lead to immune dysfunction, excessive release of immune cells and inflammation known as a cytokine storm (CS).[1] CS can have devastating effects on the host. CS can include severe inflammation, coagulopathy, hemodynamic instability, multiple organ dysfunction and even death.[5] Inflammation brought on by the innate and adaptive immune systems are critical but, excessive responses as seen with CS can have lethal consequences.

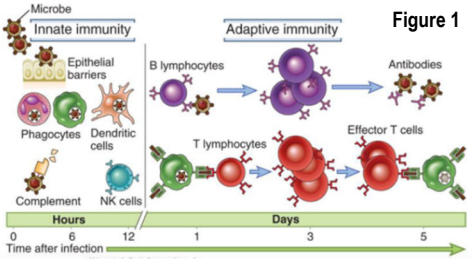

Figure 1

CS was first eluded to by William Osler in 1904 in his book, *The Evolution of Modern Medicine*, where he observed that consequences of sepsis were not directly due to the infecting pathogen but had more to do with the host's immune response to the pathogen.[6] The first citation of CS in the literature was described in 1993 on the effect of IL-1 during an acute graft-versus-host disease post-transplant.[7] Then, in 1996, CS was linked to multiple organ dysfunction syndrome (MODS) in sepsis and surgical infections.[8]

CS can be triggered by several disease states including, but not limited to, genetic disorders, autoimmune disease, malignancy, pharmacologic therapy, and infection. Likewise, there are many different cytokines thought to be important contributors to CS. While not a complete list, it has been suggested that interferon (IFN), tumor necrosis factor (TNF), IL-1, IL-6, IL-10, IL-12, and IL-17 are very likely to contribute to full-blown CS but, depending on the trigger or disease state, different cytokines may be present at greater levels than others.[9]

Table 1 Major Types and Actions of Cytokines

Type	Action	Examples
Interferons (INF)	Regulation of innate immunity, activation of antiviral properties	IFNα, IFNβ, IFNγ
Interleukins (IL)	Growth and differentiation of leukocytes, many are proinflammatory	IL-1, IL-2, IL-4, IL-6
Chemokines	Control of chemotaxis, leukocyte recruitment	CCL2, CXCCL8
Tumor necrosis factor (TNF)	Proinflammatory, activates cytotoxic T lymphocytes	TNFα, TNFβ

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Noteworthy Cytokines that contribute to CS

Type I IFNs (IFNα and IFNβ) are thought to assist with cascades that limit viral spread and infection. They activate cascades for phagocytosis and clearance in addition to activating target cells within adaptive immunity which subsequently produce more inflammatory mediators.[10,11] Type I IFNs stimulate lymphocytes which in turn increase the production and release of IFNγ. Type II IFN (IFNγ) is critical to both innate and adaptive immunity and is a key player in CS. It is a proinflammatory cytokine and is the primary activator of macrophages. Type III IFNs activate pathways to increase immune response, similar to type I IFNs. Overall, IFNs indirectly orchestrate a great deal of inflammation.[11]

IL-1 is released early on in the inflammatory cascade to activate target cells and produce other inflammatory mediators.[10,12] IL-6 is released later on and has both pro-inflammatory and anti-inflammatory properties.[10] IL-6 is responsible for transitioning from innate immunity to adaptive via turning down neutrophil activity and increasing monocyte and T cell activity. High serum levels of IL-6 can be an indicator of severe disease but, knocking out IL-6 can result in an increase in viral replication and high mortality rates.[11,13] The proinflammatory nature of IL-6 has been shown to decrease NK and cytolytic CD8 T cells to lyse infected antigen presenting cells (APC). This causes a prolonged cell to cell interaction propagating the proinflammatory environment.[14] IL-4 and IL-10 are considered anti-inflammatory and downregulate the proinflammatory activities of other cytokines. IL-17, a proinflammatory cytokine, is produced by T cells and triggers production of other inflammatory mediators such as IL-1 β, IL-6, and TNF- α.[10]

The tumor necrosis factor (TNF) family is a group of proinflammatory cytokines that induce apoptosis, initiates necrosis, and mediates inflammation in response to host intrusion.[15]

Several disease states that can result in CS are described in greater detail below:

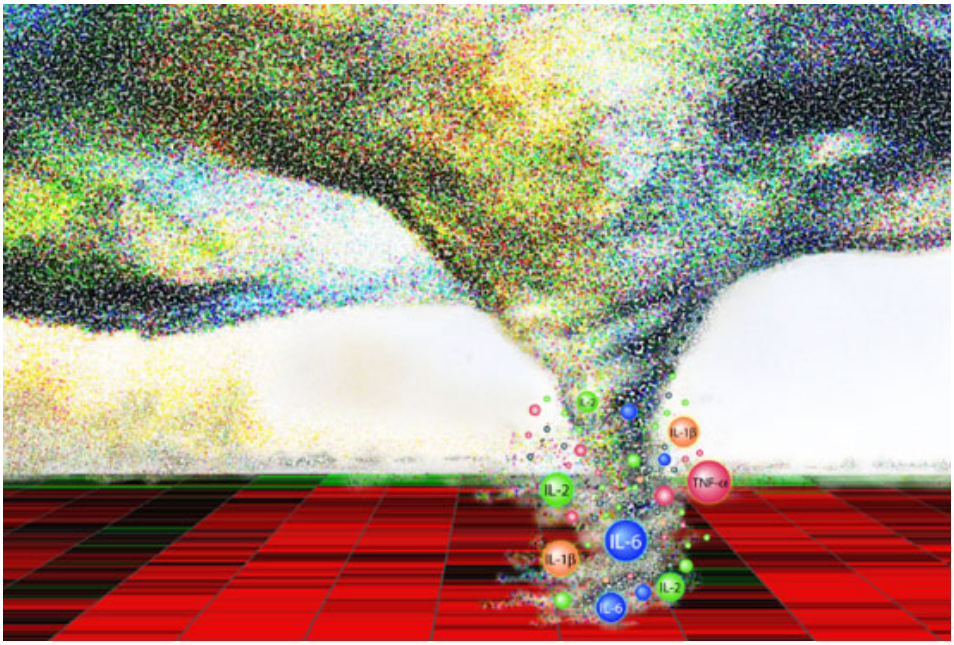
Hemophagocytic lymphohistiocytosis (HLH) is a rare genetic disorder with a high mortality rate where the host is deficient in cytotoxic cell function and viral clearance. Mutation occurs in the cytolytic pathways affecting the ability of NK and CD8 T cells to destroy virus infected host cells. Initially, upon infection, cytokines are released to signal the NK and T cells to clear the virus but, due to a genetic mutation, they are unable to destroy the virally infected cells. In turn, cytokines such as IFNγ continue to be produced because the virus is not being cleared. This process produces excessive inflammation and continued signaling of immune cells, resulting in CS.[16]

HLH can be classified as either familial (fHLH) or secondary. fHLH primarily occurs in infants where an initial infection will trigger an uncontrolled inflammatory response leading to CS and ultimately death, if untreated.[17] Secondary or acquired HLH (which does not have any identifiable genetic mutations) is less severe compared to fHLH, commonly triggered by viral infection and occurs primarily in adults.[16] While the infection itself does not cause injury to the host, it is the host's inability to clear the virus and hyperinflammatory response that causes damage.

Diagnosis is made by identifying at least 5 of 8 criteria: fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low/absent NK-cell-activity, hyperferritinemia, and high-soluble interleukin-2-receptor levels.[18] Treatment of HLH includes identification and treatment of the infectious pathogen followed by cytoablative chemotherapy and broad-spectrum immunosuppression targeting T cell activation and proliferation. Either an 8-week induction therapy of dexamethasone, etoposide, and intrathecal methotrexate (for CNS involvement only) or corticosteroids and antithymocyte globulin (ATG) can be used. Both treatment options should be considered a bridge to allogenic bone marrow transplant (BMT) in patients with fHLH. Secondary HLH patients do not typically require BMT.[16,17,18,19]

Macrophage Activation Syndrome (MAS) is another type of CS. MAS is not triggered by infection but rather by autoimmune disorders such as systemic juvenile idiopathic arthritis (sJIA), adult onset Still's disease, systemic lupus erythematous, and Kawasaki disease.[17,20] Presentation of MAS includes fever, hepatosplenomegaly, pancytopenia, hyperferritinemia, and hypercytokinemia. While the exact mechanism of MAS is not completely understood, it has been suggested that exaggerated toll-like receptor (TLR) stimulation leads to the activation of proinflammatory cytokines IL-1 and IL-18, and expansion of IFNγ producing lymphocytes may contribute to the development of this CS.[17] Others have suggested that there may be a defect in cytotoxic functions, similar to HLH.[19] What is clear is that there may be multiple pathways for MAS to develop in patients with autoimmune disorders.

No universal diagnostic criteria or lab test exist for MAS, however, some clinicians rely on the HLH diagnostic guideline to assist with diagnosis.[18] Treatment for the disorder has not been standardized and is considered controversial. Treatment with corticosteroids



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(IV methylprednisolone 30 mg/kg (max dose 1 g) or cyclosporine A is common, and using the pharmacologic treatments for HLH have also been used. Additionally, the use of anakinra, a recombinant IL-1 receptor antagonist, may be beneficial, or using other targeted cytokine therapies that block IL-6, IL-18, and IFNγ. However, clear treatment guidelines remain elusive for MAS.[16,17,19,21,22]

Malignancy Associated Syndrome of Hyperinflation (MASH) is considered CS triggered by malignancy and can occur in patients with leukemias and lymphomas. The mechanism for this CS is thought to be caused by neoplastic cells producing macrophage activating cytokines such as IFNγ which then go on to cause a hyperinflammatory response. Treatment of MASH includes supportive measures and treatment of the underlying malignancy.[19]

Cytokine Release Syndrome (CRS) is yet another CS that can occur in cancer patients treated with CAR-T (Chimeric Antigen Receptor T cell) therapy and is associated with the overproduction of cytokines from activated CAR-T cells. Mild CRS can present with flu-like symptoms such as fever, fatigue, headache, rash, arthralgia, and myalgia which can be self-limiting. Severe CRS can present with hypotension, high fever, circulatory shock, vascular leakage, disseminated intravascular coagulation, and multiple organ failure.[23] High CRP, cytopenias, elevated creatinine and liver function tests are common in CRS. Severe cases of CRS can mimic HLH and MAS. IL-6, LI-10 and IFNγ are cytokines that are consistently elevated in the serum of patients with CRS and contribute to many of the symptoms associated with the disorder.[23] Treatment for this condition can include supportive therapy, corticosteroids, and use of the IL-6 antagonist, tocilizumab.[17]

CS can be triggered by infectious diseases. Pathogens can include bacterial, viral, fungal, and protozoal. For this next section, we will focus on 4 viral infections that can cause CS, including Ebola, dengue, influenza, and the human coronaviruses.

Ebola virus (EV) is a rare but fatal zoonotic disease that is transmitted from animal to person or person to person via bodily fluids. EV is not an airborne virus. Typical presentation includes fever, flu-like symptoms, myalgias, nausea, vomiting, impaired coagulation, bruising, and blood in the urine or feces. In severe cases, patients may experience organ necrosis and hemorrhaging into the skin and mucous membranes thought to be part of EV CS.[24] Ebola has been documented to cause CS and proinflammatory cytokines in fatal Ebola cases have been identified as IL-1, IL-6, IL-8, and TNF-α.[25] It has also been found that EV can inhibit IFNα/β, which is part of the innate antiviral immune response. EV can also inhibit DC maturation which negatively affects their ability to present antigen to the adaptive system. This, in turn, alters part of the negative feedback loop of the cytokine cascade.[26] Treatment for EV is limited to supportive care as there is no proven treatment to date. Additionally, there is no vaccine for this virus. Other treatments currently being evaluated for EV CS include blood products and experimental immune therapies.[27,28] More information needs to become available regarding effectiveness of these therapies prior to establishing a more robust treatment guideline.

Dengue virus (DV) is a vector borne disease transmitted by mosquitos in warm tropical climates. DV is currently the fastest growing communicable disease with a 400% increase in infection over a recent 13-year period.[29] There are 4 known dengue virus serotypes that can lead to a spectrum of symptoms ranging from asymptomatic infection to severe disease. There are 3 different manifestations of dengue: dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). DF, also known as 'breakbone fever' (due to severe muscle and joint pain) can present with arthralgia, myalgia, headache, skin rash, and fever. In addition to the symptoms seen in DF, DHF can present with hemorrhage, plasma leakage and thrombocytopenia. DSS presents with symptoms from both DF and DHF, plus circulatory failure, hypotension and systemic shock syndrome.[24] Severe DV infection can lead to an exaggerated host immune response resulting in CS. Cytokines TNFα and IFNγ may be associated with severe forms of dengue CS and have been used to predict disease severity.[30] Other cytokines that have been found to be elevated in dengue CS are IL-6, IL-8, and IL-10. Treatment for DV is limited to supportive care as there is no proven treatment to date. Additionally, there is no vaccine for this virus. Unproven treatment approaches used for DV CS include suppression of cytokine levels with immune therapy products and the use of doxycycline for its effects on inflammatory cytokines, although the mechanism by which doxycycline affects cytokines is not completely understood.[31] Recovery from DV results in lifelong immunity to the specific serotype the host recovered from. However, if the host is later infected with any of the other 3 serotypes, outcomes tend to be worse and disease presentation is often more severe.[29]

Extreme innate immune responses or CS correspond with an increase in morbidity and mortality when considering respiratory viral illnesses such as influenza or human coronaviruses (hCoV).[32,33,34] These viruses are capable of infecting cells lower in the respiratory tract which can compromise lung function causing pneumonia, acute lung injury (ALI), and acute respiratory distress syndrome (ARDS) in the most severe cases.

Influenza virus is a respiratory illness that causes seasonal epidemics. Influenza and pneumonia were listed as the 8th leading cause of death in the United States during 2017 with 55,672 deaths reported that year.[35] Influenza typically presents with fever, cough, sore throat, myalgias, and malaise. Severe infections can cause pneumonia, ALI, ARDS, and even death. The virus initially targets the

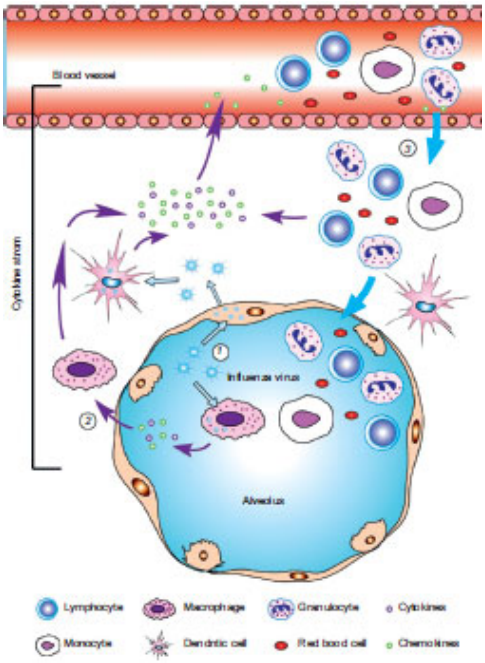

Figure 2 Cytokine storm in the lung following severe influenza infection. (1) Viruses infect lung epithelial cells and alveolar macrophages to produce progeny viruses and release cytokines/chemokines (mainly contains interferons). (2) Cytokine/chemokine-activated macrophages and virally infected dendritic cells lead to a more extensive immune response and the initiation of cytokine storm. (3) Released chemokines attract more inflammatory cells to migrate from blood vessels into the site of inflammation, and these cells release additional chemokines/cytokines to amplify cytokine storm.[12]

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respiratory tract where epithelial cells and alveolar macrophages are infected in order to carry out viral replication. Cytokines are released to target cytokine activated macrophages, monocytes, and dendritic cells to initiate an immune response within the alveolar spaces. These cells create a positive feedback loop releasing additional cytokines to signal other immune cells into the area of infection. (Figure2)[12] The excessive release of cytokines and infiltration of immune cells can cause CS resulting in alveolar damage, hyaline membrane formation, fibrin exudates, and fibrotic healing. If the damage is severe enough, the host may experience ALI or ARDS - consequences of CS within the lung alveolar space. CS caused by influenza is associated with uncontrolled proinflammatory responses and worse outcomes in patients.[6] IL -1 and TNF have been identified as two proinflammatory cytokines in patients with acute viral lung damage.[5] If the cytokine response is extreme it may even spill over from the local area of infection (lung) into the blood stream, causing a systemic CS, placing the patient at risk for MODS.[1,12] Highly virulent strains of influenza are more likely to cause severe disease resulting in acute hypercytokinemia and higher mortality rates as seen with the 1918 Spanish Flu pandemic.[32,34,36] Influenza vaccines do exist as do antiviral treatments although the most effective way to prevent infection is through vaccination. If infection does occur, treatment with a neuraminidase inhibitor or a polymerase acidic (PA) endonuclease inhibitor can be given to patients who have been symptomatic for no more than 48 hours. For more severe cases requiring hospitalization, supportive measures and treatment with the antivirals previously listed are first line. Other unproven treatments for influenza CS using an immunomodulatory approach include corticosteroids (controversial), peroxisome proliferator-activated receptor agonists (PPARs - gemfibrozil, rosiglitazone, pioglitazone), sphingosine-1-phosphate receptor 1 (SIP1) agonists, COX-2 inhibitors, antioxidants, anti-TNF therapy, intravenous immunoglobulin (IVIG) therapy (concentrated globulin from pooled human plasma), ACEIs, and ARBs[12]

Human coronaviruses (hCoVs) are a large group of respiratory illnesses that include SARS-CoV (Severe Acute Respiratory Syndrome), MERS-CoV (Middle Eastern Respiratory Syndrome), SARS-CoV 2 (Severe Acute Respiratory Syndrome 2) or COVID 19, and even the common cold. Similar to the other viruses discussed, hCoVs can present on a spectrum ranging from asymptomatic infection to severe illness. Fever, dry cough, dyspnea, and other flu-like symptoms are common hallmarks of symptomatic hCoVs with more severe cases causing pneumonia or hyperinflammatory responses such as ALI and ARDS.[24,37] Virus induced cytopathic effects, viral evasion and rapid replication, delayed host IFN response (due to viral evasion), and monocyte-macrophage and neutrophil accumulation (source of cytokine production) are thought to contribute to hCoV severity and development of CS.[37] Patients with SARS-CoV CS were found to have diffuse alveolar damage, alveolar hemorrhage, pulmonary fibrosis with inflammation and hypercytokinemia.[1,37] Proinflammatory cytokines found in patient serum with severe SARS-CoV infection include IL-1, IL-6, IL-12, and IFN-γ.[37,38] Consequences of hCoV CS can be dire resulting in respiratory failure, ARDS and even MODS. Treatment for hCoV infection is limited mainly to supportive care, however, recent use of the antiviral medication remdesivir has been shown to have inhibitory effects on hCoVs, including SARS-CoV, MERS-CoV, and SARS-CoV 2.[39] Currently, there are no available vaccines for these viruses, however, multiple trials are currently underway to bring a SARS-CoV 2 vaccine to market. Unproven treatment approaches used for hCoV include, but may not be limited to, corticosteroid therapy, IVIG, IL-1 and IL-6 inhibitors and interferons.[40]

CS treatment is complex, and the first line approach should be identification of the trigger and treatment of the underlying cause: antibiotics or antivirals for infection; treatment of the underlying disease in autoimmune disorders; and allogenic BMT in fHLH patients. Other therapies mentioned in the literature include anti-inflammatory and immune modulating medications. Anti-inflammatory medications include, but may not be limited to, corticosteroids, COX-2 inhibitors, and antioxidants. Immune modulating agents aim to inhibit inflammatory cytokines in order to dampen the immune response. Examples include IFNγ blockade, IL-1 blockade, IL-6 blockade, and TNF blockade. Therapeutic use of cytokines to treat CS associated with infection, autoimmune disease, sepsis, or malignancy may seem like a good approach but, because endogenous cytokines often have rapid, local, and pleiotropic effects, finding the right understanding of their mechanisms and how to use exogenous treatment has proven to be difficult. More studies are required to determine the place that these therapies have in treatment.

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