Making Sense of the Cytokine Storm: A Conceptual Framework for Understanding, Diagnosing, and Treating Hemophagocytic Syndromes

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KEYWORDS

• Cytokine storm • Macrophage activation syndrome
• Hemophagocytic lymphohistiocytosis • Sepsis

OBJECTIVES

After reading this article, the reader should be able to:
1. Identify clinical similarities and differences between the variety of cytokine storm syndromes
2. Describe the clinical and immunologic hallmarks of macrophage activation syndrome and hemophagocytic lymphohistiocytosis
3. Describe a pathoetiologic framework for understanding cytokine storm syndromes.

THE FINAL COMMON PATHWAY

History

In the days before germ theory, the term sepsis (from the Greek *sepo*, "I rot") was applied to all states of uncontrolled inflammation. Today, sepsis is reserved to refer to overwhelming inflammation in the context of a systemic infection (although even this definition can be ambiguous). The term cytokine storm syndrome (CSS) was developed to accommodate the observation that multiple inflammatory causes can result in a disease that appears similar to sepsis. The unifying feature of CSS is

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a clinical and laboratory phenotype suggestive of massive inflammation, progressing to multiple organ dysfunction syndrome (MODS) and eventually death, a final common pathway.

Examination and Laboratory Findings

The clinical constituents of this pathway can include fever, tachycardia, tachypnea, hypotension, malaise, generalized swelling, altered mental status, diffuse lymphoadenopathy, organomegaly (particularly of the liver and spleen), and often erythematous or purpuric rash. In response to the desire by intensive care practitioners to standardize hemodynamic management of CSS, criteria for systemic inflammatory response syndrome (SIRS) were proposed in 1992[1] and have been amended several times, notably to accommodate pediatric practice (**Table 1**).[2]

CSS also have several common laboratory abnormalities. Hematologic parameters like leukocytosis or thrombocytosis can indicate the acute phase response. Alternatively, increased cell counts can decrease precipitously as a feature of nearly all CSS, suggesting consumption. Clinicians can also take advantage of a host of nonspecific acute phase reactants, including erythrocyte sedimentation rate (ESR), C-reactive protein, procalcitonin, serum amyloid A, ferritin, and fibrinogen among others. Akin to acute cytopenias, an acute decrease in ESR and fibrinogen is most associated with macrophage activation syndrome (MAS), but can be seen in any CSS and often suggests active disseminated intravascular coagulopathy (DIC). Screens for coagulopathy such as fibrin split products and d-dimer are often increased in CSS even in the absence of overt DIC, suggesting subclinical endothelial activation. Likewise, hypoalbuminemia is frequently observed and likely represents systemic capillary leak. Routine testing often reflects various organs in distress, including the liver, pancreas, and kidneys. Such tests are rarely capable of distinguishing direct inflammatory damage from that induced by insufficient oxygen delivery.

The Elusive Hemophagocyte

Hemophagocytes are activated macrophages seen histologically to be have engulfed other hematopoietic elements (erythrocytes, leukocytes, or platelets (**Fig. 1**)).

Table 1
Pediatric SIRS criteria

	SIRS
Presence of at least 2 of the following 4 criteria Must include abnormal temperature or leukocyte count	
Core temperature	>38.5°C or <36°C
Abnormal heart rate	>2SD more than normal for age[a] or unexplained persistent increase over 0.5-h to 4-h period, or for children <1 year old: heart rate <10th percentile for age[a] or unexplained persistent heart rate depression over a 0.5-h period
Respiratory rate	>2SD more than normal for age or acute requirement for mechanical ventilation
Leukocyte count	Increased or depressed[b] for age or >10% immature neutrophils

[a] Not explained by external stimuli or drugs.
[b] Not caused by chemotherapy-induced leukopenia.
Adapted from Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6(1):4; with permission.