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"Shedding Light On Cytokine Storm" – A Review

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ABSTRACT: ***The concept of cytokine storm is increasing popularity with the introduction of immunotherapy in various diseases most notably in cancer therapy. So the basic knowledge about this topic has to be acquired by any health care professionals. Thus in this review article we dealt about the different cytokines associated with cytokine storm, its pathophysiology especially which is caused by influenza, SARS-Cov, dengue virus infections. We discussed about different grading system in relation to the syndrome associated with cytokine storm and management related to it.***

KEYWORDS: Cytokine, Cytokine storm syndrome, immunoparalysis, interferon

INTRODUCTION:

Cytokine Storm is a fancy name for hyperactive immune response in a body under the influence of any type of infections be it bacterial, fungal or parasitic or it can be due to genetic mutations or autoimmune disorder. This term first came into the light in the year 1993 with the article "Graft versus Host disease". Immune system fails to restrain cytokines when it becomes too abundant thus increasing the unnecessary immune activity. They spread uncontrollably and start destroying the healthy tissues, feeding on the red and white blood cells eventually damaging the organs. Blood pressure drops as lung becomes saturated with fluid as a result of leaky blood vessels. Clotting of blood takes place thus restricting the blood flow. As a result of which multiple organs get devoid of blood and permanent damage may occur often resulting in untimely death. Symptoms as being described by Dr. Randy Cron, a pediatric, rheumatologist and immunologist in the University of Alabama at Birmingham and co-editor of the 2019 textbook ***Cytokine Storm Syndrome*** to be like fever, certain neurological manifestations like headache, seizure,coma can be seen in most of the patients suffering from this particular condition. Goal of this review is to better understand the onset of cytokine storm along with the biological consequence of cytokine overproduction.

CYTOKINES:

Keeping up the capacity of the immune cells in an organized and a self-restricted way is Cytokines significant capacity as molecular messenger.[1] Cytokines not just liable for the development of inflammatory cells towards the site of aggravation yet additionally they affect different encompassing cells in the microenvironment. They are liable for setting off the collagen blend and cycle of re-epithelization which thus help in tissue fix and mending in the zones of inflammation.[2] In the midst of the various elements of cytokines not many of them resemble the control of cell multiplication and separation and the guideline of angiogenesis and insusceptible and fiery reactions. Various elements of cytokines are enrolled in Table 1[1].The complex organization of the cytokine reaction can be viewed as best as a progression of covering organizations, every one of which is related with a level of repetition and with substitute pathways. Despite the fact that numerous diseases out there are described extensively by comparative cytokine profiles, their clinical appearances can change. Before setting off to a point

by point conversation of cytokine storms, it merits taking a peep at the cytokines which is at the core of the cytokine storm.

MAJOR TYPES AND ACTIONS OF CYTOKINES; TABLE NO. 1

Types	Actions
Interferons	Regulating innate immunity,activating antiviral properties, anti-proliferative effects.
Interleukins	Growth and differentiation of leukocytes; many are Pro-inflammatory
Chemokines	Control of chemotaxis, leukocyte recruitment; many are proinflammatory
Colony-stimulating factors	Stimulation of hematopoietic progenitor cell proliferation and differentiation
Tumor necrosis factor	Proinflammatory, activates cytotoxic T lymphocytes

CYTOKINES ASSOCIATED WITH CYTOKINE STORM:

(A)INTERFERON: The group of cytokines that assume a focal function in intrinsic invulnerability to infections and other microbial microorganisms [3, 4] are the interferons (IFNs). Their grouping depends on their receptor explicitness and can be partitioned into three significant sorts (types I, II, and III). Type I, II and Type III or Lambda IFNs tie to their particular receptors which prompts in the commencement of downstream flagging falls, bringing about the initiation of record variables and many IFN-invigorated qualities are actuated. These qualities encode protein items with antiviral, antiproliferative, or immunomodulatory properties. Hence it got conceivable to place these impacts in helpful utilization of IFNs (regularly in blend with different medications) in the treatment of viral maladies, for example, hepatitis C and hepatitis B, specific sorts of leukemia and lymphoma, and numerous sclerosis [5, 6].

(B) INTERLEUKINS: In contrast to IFNs, the interleukins falls under assorted group of invulnerable framework controllers whose essential capacity is insusceptible cell separation and initiation. They can be either genius or calming yet like all cytokines, produce a wide scope of reactions. Proinflammatory cytokines like IL-1 and IL-1 through both immediate and roundabout components intervene the host reaction to infection[7]. These specific cytokines are dependable in expanding intense stage flagging, dealing of insusceptible cells to the site of essential

contamination, epithelial cell initiation, and optional cytokine creation. The intense stage reaction to disease brings about a wide scope of nearby impacts and foundational modifications that are proven in changes that are commonly proinflammatory, for example, ascend in explicit cytokine creation, that can be connected to viral leeway, for example, increments in complement [8]. IL-1 receptor flagging is liable for intense lung immunopathology however expands the endurance of mice tainted with flu infection by upgrading IgM neutralizer reactions and enrolling CD4 Lymphocytes to the site of infection [9].

(C) CHEMOKINES: Chemokines is viewed as the biggest family in cytokines. These are little emitted proteins and are ordered based on dividing of their initial two cysteine buildups into four kinds (CXC, CC, C, and CX3C), These chemokines go about as chemoattractants hence they control the relocation of cells, explicitly those of the invulnerable framework, and add to such various cycles as embryogenesis, natural and versatile resistant framework advancement and capacity, and disease metastasis [10]. Since these chemokines are delivered by an assortment of cells in light of infection (or other microbial) contamination in this way lion's share of chemokines are viewed as proinflammatory. The arrival of proinflammatory chemokines brings about the enlistment of insusceptible framework cells (neutrophils, monocytes/macrophages, and lymphocytes) to the site of contamination. While most cytokines have pleiotropic impacts, chemokine enrollment of resistant cells can be exceptionally particular for explicit cell types. For instance, CXCL8 (IL-8), CCL2 (monocyte chemoattractant protein 1 [MCP-1]), and CCL11 (eotaxin) are major chemoattractant factors for neutrophil, monocyte, and eosinophil insusceptible cells, separately. Chemokines and their receptors have been vigorously focused by the drug business, yet with restricted success [11].

(D) CSFs : Colony- stimulating factors (CSFs, for example, granulocyte macrophage settlement animating element (GM-CSF), macrophage state invigorating element (M-CSF), and granulocyte colonystimulating factor (G-CSF), animate hematopoietic begetter cell multiplication and separation. Province animating variables are likewise connected with aggravation, and there is proof that these components might be important for a commonly needy proinflammatory cytokine network that incorporates IL-1 and tumor necrosis factor (TNF) [12]. It is believed that by working to expand the quantity of cytokine-delivering macrophages at a site of irritation, province invigorating variables might be essential for an intensification course that serves to propagate inflammatory reactions.

(E)TNFs: First utilization of "Tumor necrosis factor" was as a cytotoxic serum factor which are equipped for initiating tumor relapse in mice [13] in as right on time as 1975, that not long after was accounted for to assume a significant function in pathogenesis of malaria and sepsis [14, 15, 17].TNF is presently viewed as a focal cytokine in intense viral infections, including those brought about by flu infection, dengue infection, and Ebola infection. TNF just as TNFR1, gives off an impression of being communicated by all cell types, guaranteeing boundless impacts of this cytokine Abundance TNF creation is related with various constant fiery and immune system infections, and TNF inhibitors have been endorsed for the treatment of inflammatory bowel disease, psoriasis, and rheumatoid arthritis [18, 19]. Interestingly, the utilization of TNF inhibitors for the treatment of sepsis has not been effective [20], perhaps because of the early delivery and short flowing half-existence of the cytokine [15].

GRADING SYSTEM OF CRS [16] : With widely increasing popularity of several immune-based therapies for cancer because of their potency and respective efficacy, optimal management of their unique toxicities equally becoming important. **Cytokine release syndrome** (CRS) is a life-threatening toxicity which occurs as a result of administration of natural and bispecific antibodies and, recently due to the increasing use of T-cell therapies for cancer. It is a non–antigen specific toxicity that occurs as a result of high-level immune of activation.
A grading system was designed by The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0) in CRS and associated with antibody therapeutics (Table 2)

Table 2. Clinical signs and symptoms associated with CRS (Cytokine Release Syndrome)

ORGAN SYSTEMS	SYMPTOMS
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia 6 bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor,dymetria, altered gait, seizures

Later it has been modified to define mild, moderate, severe, and life-threatening CRS irrespective of the inciting agent and guide to treatment recommendations (Table 3). Because many patients with CRS have overlapping symptomatology due to fever and neutropenia, infection, tumor lysis syndrome, or other medical complications, it is essential that attribution be carefully considered. [16]

Table 3. CRS revised grading system

GRADES	TOXICITY

GRADE-1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise
GRADE-2	Symptoms require and respond to moderate intervention Oxygen requirement ,40% or Hypotension responsive to fluids or low dose2 of one vasopressor or Grade 2 organ toxicity
GRADE-3	Symptoms require and respond to aggressive intervention Oxygen requirement $40% or Hypotension requiring high dose* or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis
GRADE-4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
GRADE-5	Death

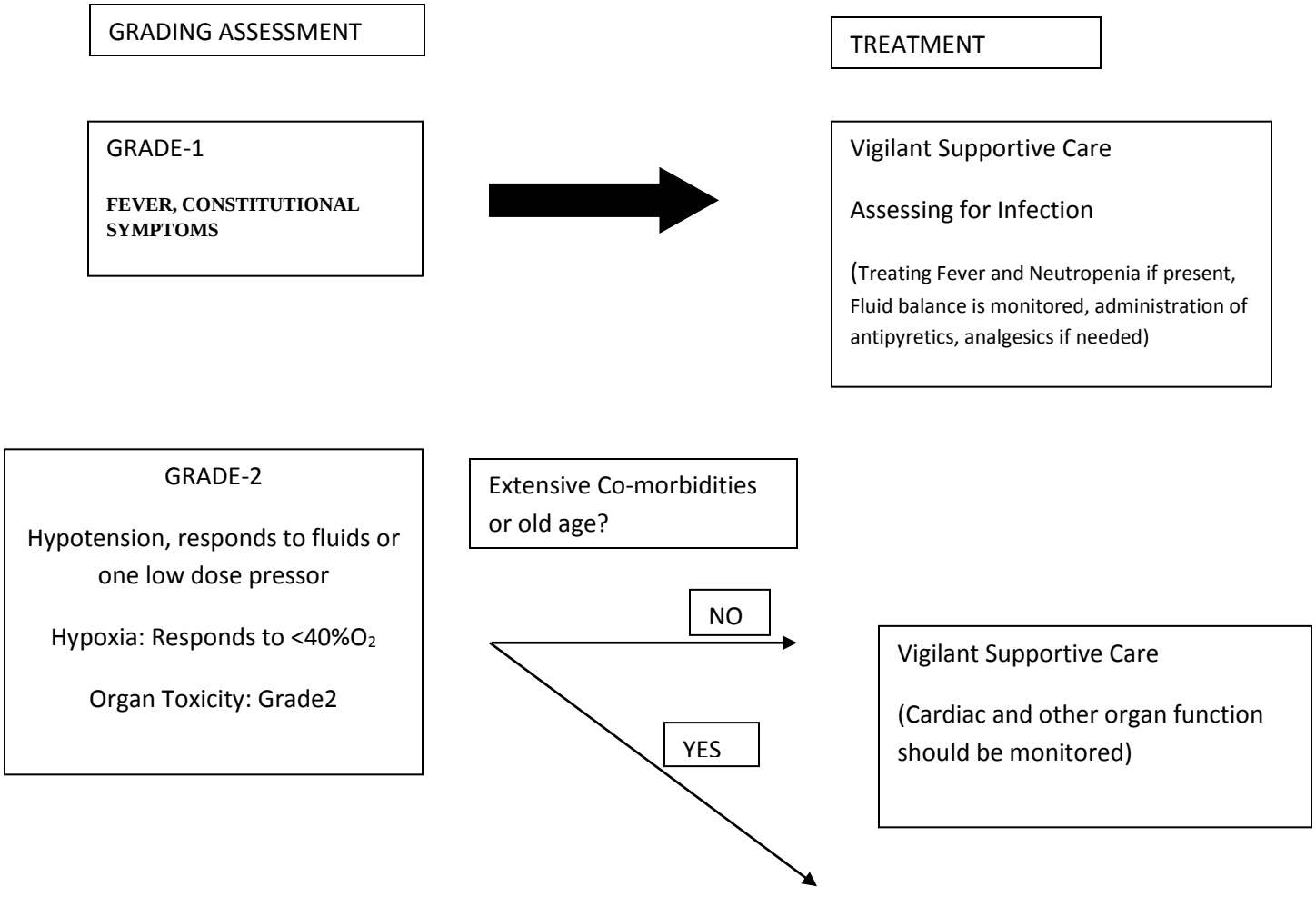
CYTOKINE STORM PATHOLOGY:

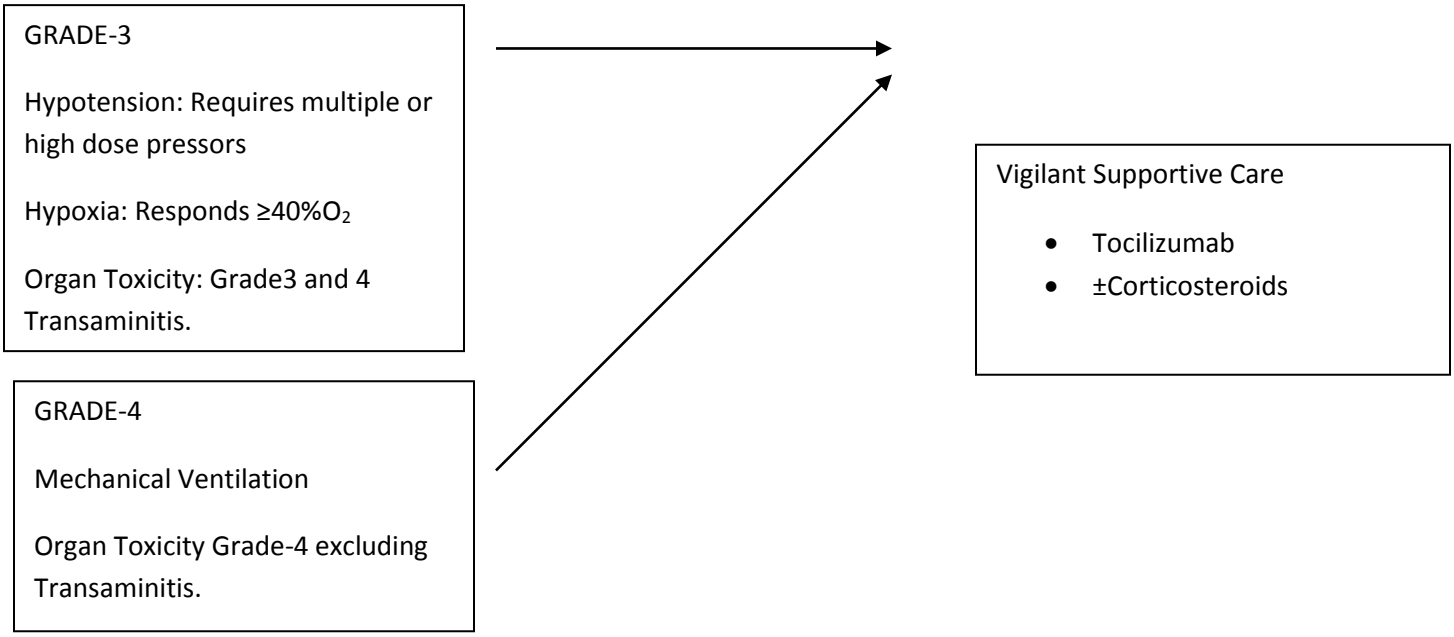
Cytokine storm related irritation starts at a neighborhood site and spreads all through the body by means of the fundamental flow. Signs of intense irritation are separately Rubor (redness), tumor (expanding or edema), calor (heat), dolor (torment), and "functio laesa" (loss of capacity). These reactions when are confined in skin or other tissue, increment blood stream, empower vascular leukocytes and plasma proteins to reach extravascular destinations of injury, increment neighborhood temperatures , and create torment, in this way goes about as a notice to the host of the nearby reactions. However, now and then these reactions regularly happen at the use of nearby organ work, especially when tissue edema causes increment in extravascular pressures and a reduction in tissue perfusion. Not long after aggravation starts fix measure additionally begins as a compensatory component, and as a rule the fix cycle gets fruitful in reestablishing appropriate capacity of tissues and organs. Then again for the situation when in some cases nearby tissues get harm because of extreme aggravation ordinarily set off by essential etiological specialist, mending happens with fibrosis, consequently bringing about relentless organ brokenness. Intense lung injury (ALI) is a typical outcome of a cytokine storm in the lung alveolar climate and fundamental course and is most normally connected with suspected or demonstrated contaminations in the lungs or different organs [21] .In people, ALI can be properly depicted as an intense mononuclear/neutrophilic fiery reaction followed by an ongoing fibroproliferative stage set apart by reformist collagen affidavit in the lung. Microorganism incited lung injury can advance into ALI or its more serious structure, intense respiratory trouble condition (ARDS), as observed with SARS-CoV and flu infection diseases. The cytokine tempest can be

commonly clarified by serious lung diseases, which is described by spilling of nearby aggravation all over to the fundamental course, bringing about foundational sepsis, prompting tenacious hypotension, hyper-or hypothermia, leukocytosis or leukopenia, and regularly thrombocytopenia [22]. Viral, bacterial, and parasitic aspiratory diseases all reason the sepsis disorder, and these etiological operators are hard to separate on clinical grounds. Sometimes, relentless tissue harm without serious microbial contamination in the lungs can likewise be seen related with cytokine storm and whose clinical appearances can mirror sepsis disorder. Aside from Intense lung diseases, the cytokine storm is likewise found as a result of serious contaminations in the gastrointestinal plot, urinary parcel, focal sensory system, skin, joint spaces, and different destinations. The beginning of a cytokine storm is trailed by foundational creation of IL-10 is viewed as a marker of a counter-mitigating reaction and has been named "immunoparalysis," which is related with downregulation of neutrophil and monocyte work in the fundamental dissemination [20, 23, 24] .Downregulation of fundamental aggravation may be thoughtfully helpful in controlling fundamental reactions to neighborhood contaminations [25]. In any case, it has been seen therefore that patients who don't recuperate from the immunoparalysis bite the dust in this manner even in the wake of enduring at first from cytokine storm. Patients with constant downregulation of HLA-DR (a marker of immunosuppression) on monocytes 3 to 4 days after the beginning of extreme sepsis and cytokine storm have a high death rate, recommending a reasoning for treatment to invert immunosuppression under such conditions [26].

TREATMENT:

The clinical symptomatology including CRS is a pointer of reaction in the setting of invulnerable based treatments. It stays muddled how much the cytokines intervening the symptomology are required for antitumor impacts. Subsequently, the objective of the board isn't to eradicate all proof of CRS yet to forestall hazardous poisonousness while boosting the potential for antitumor impacts. So, indicative treatment is suggested. Subsequently the administration of CRS as per evaluations of it is portrays in flowchart structure [16].





Treatment algorithm for management of CRS based on the revised CRS grading system. The algorithm uses the revised grading system for CRS to direct clinical management for patients with immunotherapy-associated CRS. Vigilant supportive care including empiric treatment of concurrent bacterial infections and maintenance of adequate hydration and blood pressure for every grade is recommended. Immunosuppression should be used in all patients with grade 3 or 4 CRS and instituted earlier in patients with extensive co-morbidities or older age.

CONCLUSION: The concept of cytokine storm is increasing popularity with the introduction of immunotherapy in various diseases most notably in cancer therapy. So basic knowledge about this topic has to be acquired by any health care professionals. Thus in this review article we dealt about the pathophysiology of cytokine storm especially as it is caused by influenza, SARS-Cov, dengue virus infections. We came to know about different grading system relation the syndrome associated with cytokine storm and management according to it.

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