EDITORIAL

Is a "Cytokine Storm" Relevant to COVID-19?

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In its most severe form, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), leads to a life-threatening pneumonia and acute respiratory distress syndrome (ARDS). The mortality rate from COVID-19 ARDS can approach 40% to 50%.[1,2] Although the mechanisms of COVID-19–induced lung injury are still being elucidated, the term *cytokine storm* has become synonymous with its pathophysiology, both in scientific publications and the media. Absent convincing data of their effectiveness in COVID-19, drugs such as tocilizumab and sarilumab, which are monoclonal antibodies targeting interleukin (IL)-6 activity, are being used to treat patients; trials of these agents typically cite the cytokine storm as their rationale (NCT04306705, NCT04322773). A critical evaluation of the term *cytokine storm* and its relevance to COVID-19 is warranted.

Cytokine storm has no definition. Broadly speaking, it denotes a hyperactive immune response characterized by the release of interferons, interleukins, tumor-necrosis factors, chemokines, and several other mediators. These mediators are part of a well-conserved innate immune response necessary for efficient clearance of infectious agents. *Cytokine storm* implies that the levels of released cytokines are injurious to host cells. Distinguishing an appropriate from a dysregulated inflammatory response in the pathophysiology of critical illness, however, has been a major challenge. To add further complexity, most mediators implicated in cytokine storm demonstrate pleotropic downstream effects and are frequently interdependent in their biological activity. The interactions of these mediators and the pathways they inform are neither linear nor uniform. Further, although their quantified levels may suggest severity of responses, they do not necessarily imply pathogenesis. This complex interplay illustrates the limitations of interfering in the acute inflammatory response based on single mediators and at indiscriminate time points.

Why has the "cytokine storm" been so closely associated with COVID-19? During the SARS epidemic caused by SARS-CoV-1, the term *cytokine storm* was described as a feature and associated with adverse outcomes.[3] Several early case series in COVID-19 reported levels of some plasma cytokines elevated above the normal range. In most cases, however, they are lower than plasma levels in previous cohorts of patients with ARDS. Interleukin-6, a proinflammatory cytokine, is a key mediator in the acute inflammatory response and the purported cytokine storm. The **Table** summarizes reported IL-6 levels in 5 cohorts of patients with COVID-19,[1,2,4-6] each with more than 100 patients, and 3 cohorts of patients with ARDS.[7-9] Although the median values are above the normal range in

Table. Plasma Levels of Interleukin-6 Reported in COVID-19 Compared With Levels Previously Reported in ARDS[a]

	Total population				Severe disease		
COVID-19	No.	IL-6 levels, pg/mL			No.	IL-6 levels, pg/mL	Measurement platform
Zhou et al[4]	191	7 (5-11)			54[b]	11 (8-14)	CL
Wu et al[1]	123	7 (6-9)			84[c]	7 (6-11)	CL
Mo et al[5]	155	45 (17-96)			85[d]	64 (31-165)	CL
Qin et al[2]	452	21 (6-47)			286[e]	25 (10-55)	CL
Cummings et al[6]	NR	NR			237[f]	26 (11-69)	CL
ARDS	Total population		Hypoinflammatory		Hyperinflammatory		Measurement platform
	No.	IL-6 levels, pg/mL	No.	IL-6 levels, pg/mL	No.	IL-6 levels, pg/mL	
ALVEOLI[7]	521	238 (94-741)[f]	386	154 (67-344)	135	1525 (584-3802)	ELISA
FACTT[8]	884	130 (46-411)[f]	638	86 (34-216)	246	578 (181-2621)	ELISA
SAILS[9]	720	443 (173-1513)[f]	451	282 (115-600)	269	1618 (517-3205)	ELISA

Abbreviations: ALVEOLI, Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury; ARDS, acute respiratory distress syndrome; CL, clinical laboratory; CLIA, chemiluminescent immunoassay; ELISA, enzyme-linked immunosorbent assay; FACTT, Fluids And Catheters Treatment Trial; ICU, intensive care unit; IL-6, interleukin-6; NR, not reported; SAILS, Statins for Acutely Injured Lungs From Sepsis.

[a] Presented values are the medians with interquartile ranges. The top segment of the Table reports data from selected COVID-19 cohorts (n > 100) and their corresponding severe subgroups. The bottom segment reports data from 3 National Heart, Lung, and Blood Institute ARDS network randomized clinical trials. Values are reported for the total cohorts and in subgroups stratified by ARDS phenotypes (hypoinflammatory and hyperinflammatory). The mean (SD) IL-6 levels for the ARDS trials were as follows: ALVEOLI, 2051 (8208) pg/mL; FACTT, 1048 (3348) pg/mL; and SAILS, 2363 (10 940) pg/mL.

[b] Nonsurvivors.

[c] ARDS.

[d] Refractory hypoxemia.

[e] Acute hypoxemic respiratory failure.

[f] Requiring ICU admission.

many (but not all) cases, they are lower than the median values typically reported in ARDS. The median values in randomized clinical trials conducted by the National Heart, Lung and Blood Institute's ARDS Network are approximately 10- to 40-fold higher, even when only patients with severe COVID-19 are considered.[7-9] The hyperinflammatory phenotype of ARDS is characterized by elevated proinflammatory cytokines, an increased incidence of shock, and adverse clinical outcomes.[7-9] The characteristics of this phenotype could be considered as most consistent with those expected with the cytokine storm. However, median IL-6 levels in patients with the hyperinflammatory phenotype of ARDS are 10- to 200-fold higher than levels in patients with severe COVID-19 (Table).

Putting the unsubstantiated theory of the cytokine storm aside, the more intriguing question to ask is why are clinical outcomes in COVID-19 so unfavorable despite relatively low levels of circulating IL-6? One hypothesis is that severe viral pneumonia from COVID-19 produces primarily severe lung injury, without the same magnitude of systemic responses in most patients with COVID-19 as reported in prior studies of the hyperinflammatory phenotype in ARDS.[7-9] For example, a recent postmortem report of patients with COVID-19 ARDS identified severe vascular injury, including alveolar microthrombi that were 9 times more prevalent than found in postmortem studies of patients with influenza ARDS.[10] Ongoing research may identify more specific mechanisms of COVID-19–mediated lung injury.

There are some limitations to these observations. Almost all the COVID-19 IL-6 data are from clinical laboratory tests. In most studies, details of the exact methods used are not available; calibration issues could lead to underestimating IL-6 levels compared with measurements based on enzyme-linked immunosorbent assay used in prior ARDS studies.[7-9] Furthermore, plasma levels of cytokines may not be representative of lung inflammation. Given the number of COVID-19 cases worldwide, the data on IL-6 levels are from a very small fraction of patients. Nevertheless, the theory of the cytokine storm is based on these data, and the case for its presence in COVID-19 seems weak. A more appropriate conclusion would be that in comparison to other causes of ARDS, COVID-19 is characterized by lower levels of circulating cytokine responses. Perhaps the most valid conclusion, however, is that the current data are insufficient to ascertain the precise role and scope of dysregulated cytokine responses in COVID-19.

Widespread acceptance of the term *cytokine storm* in COVID-19 has motivated the use of potent immunomodulatory therapies both in the setting of clinical trials and on a compassionate basis. These drugs, such as IL-6 inhibitors and high-dose corticosteroids, block pathways critical to host immune responses. Many monoclonal antibody drugs are being repurposed from treating patients with chronic inflammatory conditions where optimal pharmacokinetics demand prolonged half-lives. Long-lasting and indiscriminate suppression of inflammation in the acute critical care setting raises concerns about impaired clearance of SARS-CoV-2 and increased risk for secondary infections. Enthusiasm for the use of immunomodulatory approaches in COVID-19 seems to derive in large part from clinical experience with *cytokine release syndrome* (CRS), a term frequently interchanged with *cytokine storm*. In the 2016 study of CRS by Maude and colleagues, patients who developed CRS following treatment with chimeric antigen receptor T cells were effectively treated with tocilizumab.[11] Notably, the peak plasma IL-6 level in patients who developed CRS was approximately 10 000 pg/mL—almost 1000-fold higher than that reported in severe COVID-19. Conceivably, these therapies could be effective in COVID-19, but the likelihood for success would be enhanced by selecting the right patients with predictive enrichment and the right timing for intervention.[7]

Given reports that dexamethasone may improve survival for patients with COVID-19 and ARDS, it should be determined whether these effects differ between ARDS phenotypes and if they occur despite the absence of a circulating hyperinflammatory cytokine response. If so, the additional information about dexamethasone would further substantiate the importance of studying local inflammatory responses to COVID-19 in the lungs.

For these reasons, the term *cytokine storm* may be misleading in COVID-19 ARDS. Incorporating a poorly defined pathophysiological entity lacking a firm biological diagnosis may only further increase uncertainty about how best to manage this heterogeneous population of patients. The manifestations of elevated circulating mediators in the purported cytokine storm are likely to be endothelial dysfunction and systemic inflammation leading to fever, tachycardia, tachypnea, and hypotension. This constellation of symptoms already has a long history in critical care, known as systemic inflammatory response syndrome, and was used to define sepsis for decades. Interventions targeting single cytokines in sepsis, unfortunately, also have a long history of failure. Although the term *cytokine storm* conjures up dramatic imagery and has captured the attention of the mainstream and scientific media, the current data do not support its use. Until new data establish otherwise, the linkage of cytokine storm to COVID-19 may be nothing more than a tempest in a teapot.

ARTICLE INFORMATION

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REFERENCES

1. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. Published online March 13, 2020. doi:10.1001/jamainternmed.2020.0994

2. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. Published online March 12, 2020;ciaa248. doi:10.1093/cid/ciaa248

3. Huang KJ, Su IJ, Theron M, et al. An interferon-gamma-related cytokine storm in SARS patients. *J Med Virol*. 2005;75(2):185-194. doi:10.1002/jmv.20255

4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3

5. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis*. Published online March 16, 2020;ciaa270. doi:10.1093/cid/ciaa270

6. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395(10239):1763-1770. doi:10.1016/S0140-6736(20)31189-2

7. Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA; NHLBI ARDS Network. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med*. 2014;2(8):611-620. doi:10.1016/S2213-2600(14)70097-9

8. Famous KR, Delucchi K, Ware LB, et al; ARDS Network. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am J Respir Crit Care Med*. 2017;195(3):331-338. doi:10.1164/rccm.201603-0645OC

9. Sinha P, Delucchi KL, Thompson BT, McAuley DF, Matthay MA, Calfee CS; NHLBI ARDS Network. Latent class analysis of ARDS subphenotypes: a secondary analysis of the statins for acutely injured lungs from sepsis (SAILS) study. *Intensive Care Med*. 2018;44(11):1859-1869. doi:10.1007/s00134-018-5378-3

10. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med*. Published online May 21, 2020. doi:10.1056/NEJMoa2015432

11. Maude S, Barrett DM. Current status of chimeric antigen receptor therapy for haematological malignancies. *Br J Haematol*. 2016;172(1):11-22. doi:10.1111/bjh.13792

Product Hopping—An Expensive and Wasteful Practice

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What is the price of patient convenience or the cost of providing incentives for its delay? In this issue, Rome et al[1] report on the $4.3 billion to $6.5 billion of excess drug spending by patients, Medicare, Medicaid, and private insurers because the manufacturer of glatiramer acetate, a disease-modifying drug for multiple sclerosis that patients must take indefinitely, waited until 1 year before the expiration of the patent of their original product to reformulate it, effectively delaying full generic competition. In 2014, Teva Pharmaceuticals obtained a new patent for a double-strength, 3-times-weekly injection of glatiramer acetate (Copaxone), 40 mg, to replace daily glatiramer, 20 mg. This new formulation, which has the advantage of fewer injection reactions and greater patient convenience compared with the daily version, was first registered in a clinical trial in 2005 but was released 10 years later. There were aggressive advertisements for this new formulation, reduced rebates for the old brand name product, and a price point similar to that of the generic daily version that could enter the market when the patent expired for Copaxone in 2015. The combination of these factors allowed Teva to increase its earnings for another 2.5 years by delaying market competition that could have driven down the prices of both generic and brand name glatiramer.

Related articles pages 1165 and 1255

In 2020, Teva's 2005 study on the efficacy of double-strength glatiramer, 40 mg, still remains unpublished. Several trials by Teva registered in the interim investigated adjunctive therapies to reduce injection-site pain and topical reactions associated with daily glatiramer (including warm compresses, diclofenac gel, and antihistamines). That Teva spent years attempting to manage adverse effects with more medications and only released the patient-friendly double-strength 3-times-weekly version when patent expiration date in 2015 loomed suggests profit- rather than patient-focused practices.

After 2 years of litigation, the US District Court of Appeals invalidated the patent for Teva's 3-times-weekly version. In 2018, a 3-times-weekly generic glatiramer, 40 mg, entered the market. By 2019, the average cost of all glatiramer products for patients with multiple sclerosis decreased from $5000 per month to less than $2000 per month.[1]

Product switching (often termed *product hopping*) is not new. Rome et al[1] cite well-known cases involving isomer switching on new proton pump inhibitors for acid reflux, reformulation of opiate use disorder maintenance therapy, and rebranding of anti-Alzheimer disease medications. In contrast to encouraged improvements of an existing product, product hops can be defined by (1) manufacturer reformulation of a branded product to ensure that an imminently available generic is not substitutable and (2) manufacturer encouragement of prescriptions for a reformulated product rather than the original product. Product hops often draw less attention than exorbitantly priced novel agents because patients and the public are usually unaware of the decreased costs that should be expected with entry of generic products into the market.[2]

Patients with autoimmune conditions who require lifelong disease-modifying therapy may be particularly affected by pharmaceutical company practices that delay competition for biologics. In 2017, all of the 10 most expensive Medicare Part B medications were biologics.[3] Also in this issue, Chen et al[4] report on the delayed uptake of infliximab biosimilars. Infliximab biosimilars are used to treat disorders such as inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis psoriasis and ankylosing spondylitis. They fall under a