COVID-19 cytokine storm: what is in a name?

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It is now almost difficult to imagine back to a time before COVID-19 turned the world upside down. The pandemic has taken an enormous toll on patients, families and communities, working fundamental changes into our lives and into our thoughts. The medical community has formed one of many 'front lines' in the battle against COVID-19, and our lives and thoughts have been transformed as well. When the COVID-19 story is told, a key subplot will be how physicians and scientists responded to the virus. The report by Caricchio *et al*[1] in *Annals* gives us opportunity to consider the medical response to COVID-19, both at a practical level and with respect to the evolving concept of COVID-associated cytokine storm.[1]

These investigators confronted the pandemic at Temple University, in Philadelphia, one of the early epicentres of COVID-19 in the USA. In a period of 5 weeks beginning in March 2020, the Temple team admitted more than 500 adults with characteristic pulmonary ground-glass opacities, all requiring supplemental oxygen and most positive for SARS-CoV-2 by qPCR. Despite this onslaught, the team still managed to collect and analyse data to ask whether clinical or laboratory parameters accurately predicted the severe inflammatory phenotype referred to here as the 'COVID-19 cytokine storm' (COVID-CS). Lacking an accepted gold standard, the investigators employed a consensus of expert rheumatologists and pulmonologists to assign 64 patients (12%) to this category, on the basis of worsening respiratory status and elevation in C reactive protein (CRP), ferritin, D-dimer, lactate dehydrogenase (LDH), and/or troponin. COVID-CS criteria were then tested in a second cohort of 258 Temple patients admitted during a 12-day period later in April.

To develop their prediction model, they used univariate logistic regression to identify variables associated with COVID-CS and then principal components analysis to find predictors that clustered together, followed by an iterative computational algorithm to define optimal cut-off values. Ferritin and CRP did not add predictive power but were included in the final criteria per expert preference. The final model (we may call these the Temple Criteria) classified patients as COVID-CS based on (1) documented COVID-19; and (2) ferritin>250 ng/mL and CRP>4.6 mg/dL; and (3) one feature from each cluster: cluster I (low albumin, low lymphocytes, high neutrophils), and cluster II (elevated alanine aminotransferase, aspartate aminotransferase, D-dimer, LDH, troponin I), and cluster 3 (low anion gap, high chloride, high potassium, high blood ureal nitrogen:creatinine ratio). Of 513 inpatients, 173 met these criteria (34%, including 54 of the 64 gold-standard patients, sensitivity 0.84 specificity 0.73). In the validation cohort, experts considered 39 (15%) to have COVID-CS, while the criteria identified 85 (33%, including 27 of the 39 gold-standard patients, sensitivity 0.69 specificity 0.78).

Patients meeting the Temple Criteria demonstrated far less favourable outcomes. In the derivation cohort, they experienced a greater length of hospital stay (15.1 vs 5.7 days) and higher mortality (28.8% vs 6.6%), differences even more pronounced in the validation cohort (15.5 vs 4.7 days, 33.7% vs 4.2%). The case-fatality rate might have been even higher if the Temple group had not presciently employed corticosteroids at admission in all patients, well before the Randomized Evaluation of

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COVID-19 Therapy (RECOVERY) trial established this intervention as standard of care.[2]

Importantly, conventional cytokine storm scales proved poorly suited to identify COVID-CS. The 2004 haemophagocytic lymphohistocytosis (HLH) criteria, the H-Score and the 2016 macrophage activation syndrome (MAS) criteria each missed at least 75% of gold-standard patients, while classifying many others as positive. Thus, patients meeting conventional indices of cytokine storm overlapped little with those considered clinically to have COVID-CS.

Now that we have the Temple Criteria, what should we do with them? We should begin with two important caveats. First, patients in the derivation and validation cohorts were allocated to categories based on an average of laboratory values over the first 7 days of hospitalisation, or until diagnosed clinically with COVID-CS, whichever came first. As the authors note, only 43% of patients with COVID-CS met criteria at hospital admission, rising to approximately 80% by hospital day 10. Together with their imperfect sensitivity and specificity, the implication is that while the Temple Criteria can be used to assess patients at any point in time, they should be employed as a guide rather than as the sole basis to withhold (or to institute) treatment. Second, the therapeutic implications of meeting Temple Criteria remain to be established. It is tempting to conclude that patients with "COVID-CS" should be treated for cytokine storm. However, randomised controlled trials (RCTs) of interleukin (IL)-6 blockade for severe COVID-19 have proven essentially null, while an RCT of the IL-1 antagonist anakinra was halted for possible excess mortality and one testing the anti-IL-1β antibody canakinumab has just been terminated for futility.[3–5] These trials do not exclude the possibility that highly selected subsets of patients may benefit from these interventions, or that blockade of multiple immune pathways simultaneously could be more effective. However, they do leave uncertainity which additional therapies, if any, might benefit patients meeting the Temple Criteria.

This second caveat highlights the ongoing challenge of understanding what is going on with COVID-19. According to PubMed, the term 'cytokine storm' has been invoked in connection with COVID-19 by over 1000 publications. Many of these publications seem to take the idea of a COVID-CS for granted. Still, how sure are we really that severe COVID-19 is a cytokine storm?

A cytokine storm is a pathophysiologic situation in which mediators liberated by activated host cells trigger other host cells to build a self-reinforcing inflammatory spiral. Interrupting host–host signalling is an essential part of treatment. The best-understood cytokine storms arise through defects in lymphocyte-mediated control of macrophages. These syndromes result in the clinical and laboratory phenotype that HLH and MAS criteria were designed to detect, characterised by very high levels of ferritin (reflecting activated macrophages) and soluble IL-2 receptor (sIL-2R, reflecting activated lymphocytes), often in the context of high levels of IFNγ and its enabler cytokine IL-18.[6] Chimeric antigen receptor T cell-induced cytokine release syndrome (CRS) is somewhat different, mediated through antigen-directed lymphocyte activation that results in astonishing levels of IL-6; correspondingly, CRS responds to IL-6 antagonism, whereas many other cytokine storms do not.[7] However, neither acute COVID-19 nor its late manifestation multisystem inflammatory syndrome in children (MIS-C) quite mimics HLH, MAS or CRS. IL-6, ferritin, sIL-2R and IL-18 are elevated but levels remain relatively modest.[8–11] Transaminitis and cytopaenias are comparatively mild, aside from lymphopaenia that is likely a direct effect of SARS-CoV-2. Splenomegaly is largely absent. Corticosteroids do save lives, but the doses employed in RECOVERY pale in comparison with those typically required for conventional HLH, and their efficacy is not (known to be) restricted to patients meeting COVID-CS criteria. As noted, cytokine blockade in severe COVID-19 has yet to be proven effective. Although experience in selected patients treated with corticosteroids and anakinra is suggestive, these therapies are not specific for cytokine storm; further, sharp discordance between observational series and controlled trial data has been a recurring feature of this pandemic (see hydroxychloroquine, azithromycin, tocilizumab), emphasising the need for caution in the interpretation of anecdotal experience. The severe course of COVID-19 reported in individuals with defects in Toll-like receptor 7 or other interferon-related pathways, or with anti-interferon antibodies, underscores the importance of pathogen control.[12–14] Sometimes intense inflammation arises simply because an infection is overwhelming.

None of these considerations prove that COVID-19 does not unleash a cytokine storm; they simply highlight that the case remains open. In The Structure of Scientific Revolutions, Thomas Kuhn describes how scientists fit observations into an accepted explanatory paradigm until enough exceptions accumulate to put the model under stress; at that point, if a new and better model is available, a 'paradigm shift' occurs through which anomalous observations now become the foundation of a new world view. Kuhn's classic example is the shift from a Ptolemaic (Earth-centred) to a Copernican (Sun-centred) understanding of the solar system. The new model becomes the accepted paradigm until it, too, is upended by accumulating observations.[15] While our understanding of COVID-19 has not undergone revolutionary change to quite such an extent, we have still come a long way in a short time, growing to appreciate its remarkable age tropism, thrombotic risk, myocarditis, skin manifestations and (in children and some adults) delayed MIS-C presentation. As physicians struggling to come to terms with a new disease, we use familiar diseases to supply a provisional conceptual framework. This process of understanding by analogy has been hard at work in the current pandemic: COVID-19 is like other pandemic coronavirus syndromes, like CRS, like MAS, like Kawasaki disease, like toxic shock syndrome. These parallels allow us to extrapolate from what we already know but carry the risk that we may assume shared features even where evidence remains tenuous. As we apply the Temple Criteria, we must keep in mind that the term "COVID-CS" encapsulates a pathophysiologic hypothesis about how COVID-19 makes patients sick, rather than an established fact, and that data in support of cytokine storm as a frequent contributor to disease severity in COVID-19 seem to be getting weaker rather than stronger.

This concern notwithstanding, the creators of the Temple Criteria deserve our admiration for their thoughtful and persuasive investigation, conducted under the most trying of conditions. The Temple Criteria provide an important new tool to guide physicians in their evaluation of COVID-19 patients and a useful way for investigators to analyse datasets from observational and interventional trials, potentially helping to define patients who may benefit from specific interventions. They also push us to continue to think precisely about

the terms that we use and what they imply, and to remain on the alert for observations that may compel us toward the next conceptual paradigm in the COVID-19 pandemic.

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