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# Cytokine storm and the prospects for immunotherapy with COVID-19

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## ABSTRACT

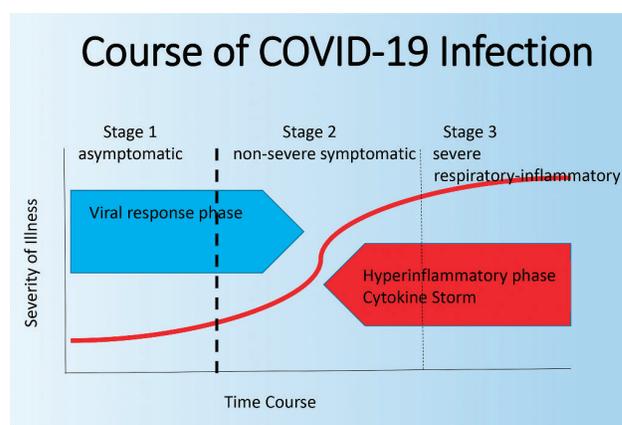
Knowledge about the pathobiology of SARS-COV-2 as it interacts with immune defenses is limited. SARS-COV-2 is spread by droplets that come into contact with mucous membranes. COVID-19 is characterized by 3 stages: asymptomatic-paucisymptomatic incubation, nonsevere symptomatic illness for 80% of those infected, and severe respiratory illness. A syndrome characterized by hypercytokinemic inflammation referred to as a “cytokine storm” can occur in patients with advanced disease. Effective antiviral agents that can prevent viral infection in exposed individuals are needed.

As we learn about COVID-19, we recognize that there are gaping holes in our knowledge of the pathobiology of SARS-COV-2 as it interacts with our immune defenses. Epidemiologically, we know that most people, especially young and healthy ones, do quite well at defending themselves from this infection and that those with severe disease tend to recover without sequelae. We also know that not everyone has a relatively benign disease course and that risk factors for progression are dominated by age and comorbidities, especially cardiovascular disease, diabetes, and obesity. While some of these clinical findings seem to have face-validity, others are not so clear. Why is age such a dominant risk factor, and why do some young, otherwise seemingly healthy individuals succumb to the infection? The answers to these questions are not completely understood.

To tackle this problem, we must first examine what is known about the pathogen host immune system interaction. SARS-COV-2 is spread by droplets that

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**Figure 1.** Three stages of COVID-19 infection.

come into contact with mucous membranes. Interestingly, not all individuals who are exposed acquire the infection. Once infected, the disease progresses through 3 main stages (Figure 1).

Stage 1 is an asymptomatic-paucisymptomatic incubation period where the virus may or may not be clinically detectable. Stage 2 is a period of nonsevere symptomatic illness with detectable virus that may resolve or progress. In infected individuals, approximately 80% will end in stage 2. Finally, stage 3 is characterized by severe respiratory illness with progressive pneumonitis that may or may not lead to respiratory failure, which in its final stages, causes diffuse alveolar damage. As discussed below, this last stage is characterized by a state of high levels of inflammation leading to further clinical deterioration and potential involvement of extrapulmonic sites such as cardiac tissue.<sup>1</sup>

Immunologically, SARS-COV-2 infects cells of the respiratory tract and likely infects endothelial cells and macrophages based on our knowledge of SARS-CoV, which shares considerable homology. Infection triggers innate immunity followed by adaptive humoral and cellular immune responses. The

development of neutralizing antibodies is believed to be a critical event in recovery as well as the generation of virus-specific T-cell responses, ultimately leading to viral clearance.<sup>2</sup> Unfortunately, the process is not linear, and we are still trying to understand why adaptive immunity fails and many infected individuals continue to be carriers of the virus.<sup>3</sup>

Attempts to correlate the stages of clinical disease described above with SARS-COV-2 viral loads from respiratory secretions, blood, and tissues have yielded conflicting results: some patients with advanced disease have high viral loads while others do not.<sup>4</sup> Recent attempts to reconcile these findings suggest that cytokine production belies many of the late-stage disease manifestations in COVID-19 disease, and this may be driven by viral infection or noninfective sources such as collateral tissue destruction.<sup>5</sup>

In patients with advancing disease, a syndrome has been reported characterized by hypercytokinemic inflammation. This syndrome has variably been referred to as “cytokine storm,” or at times, as macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH).<sup>6</sup> In COVID-19, and unlike MAS or sHLH, the primary target organ is the lung, leading to an acute respiratory distress syndrome with some shared features to the idiopathic form both clinically and pathologically.<sup>5</sup>

Laboratory features are quite similar among these disorders, with marked elevations of acute phase reactants (ie, C-reactive protein, ferritin), lymphopenia, coagulation defects, and elevated levels of numerous inflammatory cytokines; prominent among them are interleukins 6 (IL-6), 1 (IL-1), 2 (IL-2), 7 (IL-7), and 17 (IL-17), granulocyte macrophage-colony stimulating factor (GM-CSF), and tumor necrosis factor (TNF).<sup>7</sup> Why there is an increased incidence of this inflammatory late-stage complication in select young individuals and more frequently in patients who are elderly and in those with comorbidities is poorly understood. Interestingly though, 30% of individuals succumbing to H1N1 were found to carry single copies of genes commonly encountered in patients with HLH,<sup>8</sup> suggesting a link between immune predisposition to sHLH and outcome.

We can also postulate that the chronic low-grade inflammation and an increase in self-reactivity that characterize the aging immune system also may be contributory. Importantly, recent studies have demonstrated that immunologic aging proceeds at different rates in different individuals and thus, mere chronologic age is, not surprisingly, a relatively crude predictor of COVID-19 progression.<sup>9</sup>

From a therapeutic perspective, there is a clear

need for an effective antiviral agent that can prevent viral infection in exposed individuals and limit tissue damage in those with established disease (stage 1 and 2). In stage 3, in the absence of any effective antiviral therapy, we are relegated to supportive care. It is at this stage that the experimental use of agents designed to limit tissue damage driven by uncontrolled inflammation is being investigated. Given the similarities to other hypercytokinemic states, a variety of nonspecific immunosuppressive strategies are needed, such as glucocorticoids, hydroxychloroquine, colchicine, and Janus kinase inhibitors, as well as a number of targeted therapies directed at pivotal cytokines. For now, the experience with such agents largely consists of anecdotal case reports and small clinical trials.<sup>10</sup>

As of this writing, more than 270 clinical trials of various therapeutics for COVID-19 are registered at [clinicaltrials.gov](http://clinicaltrials.gov) ([clinicaltrials.gov](http://clinicaltrials.gov)). A number of agents have been proposed or are in use, including anti-IL-1, anti-GM-CSF, anti-TNF, and Janus kinase inhibitors. Among these therapies, agents targeting IL-6 have generated the greatest enthusiasm. Two such agents (tocilizumab and sarilumab) are already in multicenter randomized control trials.

IL-6 is a pleomorphic cytokine produced by both hematopoietic and viscerosomatic cells with far-reaching effects on immune function and diverse nonimmune physiologic processes.<sup>11</sup> It is a key upstream driver of inflammatory pathways and has been successfully targeted therapeutically. IL-6 also has been shown to be a predictor of respiratory failure. Targeting IL-6 with tocilizumab is now indicated for treatment of cytokine storm accompanying CAR-T cell therapy.<sup>12</sup> Clinical support for such studies has come a variety of sources, including anecdotes from now widespread use of off label tocilizumab, case reports, and small series<sup>13</sup> where rapid reversal of laboratory and clinical parameters have been reported. Balancing enthusiasm for such a strategy is the known pivotal role of IL-6 in host defense, particularly in defense against respiratory viruses.<sup>14</sup>

Above all, there are serious considerations in the timing of therapy. Administering treatment too early may compromise antiviral immunity, while waiting too long may risk irreversible organ damage. The phase 3 randomized controlled trial of tocilizumab (NCT04320615) and the phase 2/3 randomized controlled trial of sarilumab (NCT04315298) are projected to be complete within a number of months. Other novel therapies used alone or in combination include targeting IL-1, GM-CSF, granulocyte-colony stimulating factor, and Janus kinase. These have been reviewed or mentioned in several excellent narrative reviews.<sup>5,10</sup>

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