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# A Clinical-Therapeutic Staging Proposal

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# COVID-19 Illness in Native and Immunosuppressed States:

# A Clinical-Therapeutic Staging Proposal

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The onslaught of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated coronavirus disease 2019 (COVID-19) has gripped the world in a pandemic and challenged the culture, economy and healthcare infrastructure of its population. It has become increasingly important that health systems and their clinicians adopt a universal consolidated framework to recognize the staged progression of COVID-19 illness in order to deploy and investigate targeted therapy likely to save lives. The largest report of COVID-19 from the Chinese Centers for Disease Control and Prevention summarized findings from 72, 314 cases and noted that while 81% were of a mild nature with an overall case fatality rate of 2.3%, a small sub-group of 5% presented with respiratory failure, septic shock and multi-organ dysfunction resulting in fatality in half of such cases, a finding that suggests that it is within this group that the opportunity for life saving measures may be most pertinent.[1] Once the disease is manifest, supportive measures are initiated with quarantines; however a systematic disease modifying therapeutic approach remains empirical. Pharmacotherapy targeted against the virus holds the greatest promise when applied early in the course of the illness, but its usefulness in advanced stages may be doubtful.[2, 3] Similarly, use of anti-inflammatory therapy applied too early may not be necessary and could even provoke viral replication such as in the case of corticosteroids.[4] It appears that there are two distinct but overlapping pathological subsets, the first triggered by the virus itself and the second, the host response. Whether in native state, immunoquiescent state as in the elderly, or immunosuppressed state as in heart transplantation, the disease tends to present and follow these two phases, albeit in different levels of severity. The early reports in heart transplantation suggest that symptom expression during the phase of establishment of infection are similar to non-immunosuppressed individuals; however, in limited series the second wave determined by the host-inflammatory response appears to be milder, possibly due to the concomitant use of immuno-modulatory drugs.[5,6] Similarly, an epidemiological study from Wuhan in a cohort of 87 patients suggests that precautionary measures of social distancing, sanitization and general hygiene allow heart transplant recipients to experience a low rate of COVID-19 illness.[7] We do not of course, know if they are asymptomatic carriers, since in this survey-based study universal testing during the early 3 months was not employed. One interesting fact in this study was that many heart transplant recipients have hematological changes of lymphopenia due to the effects of immunosuppressive therapy which may obfuscate the laboratory interpretation of infection in such patients should they get infected.

Much confusion abounds in the therapeutic tactics employed in COVID-19. It is imperative that a structured approach to clinical phenotyping be undertaken to distinguish the phase where the viral pathogenicity is dominant versus when the host inflammatory response overtakes the pathology. In this editorial we propose a clinical staging system to establish a standardized nomenclature for uniform evaluation

and reporting of this disease, to facilitate therapeutic application and evaluate response. We propose the use of a 3-stage classification system, recognizing that COVID-19 illness exhibits three grades of increasing severity which correspond with distinct clinical findings, response to therapy and clinical outcome (Figure).

### Stage I (mild) – Early Infection:

The initial stage occurs at the time of inoculation and early establishment of disease. For most people, this involves an incubation period associated with mild and often non-specific symptoms such as malaise, fever and a dry cough. During this period, SARS-CoV-2 multiplies and establishes residence in the host, primarily focusing on the respiratory system. Similar to its older relative, SARS-CoV (responsible for the 2002-2003 SARS outbreak), SARS-CoV-2 binds to its target using the angiotensin-converting enzyme 2 (ACE2) receptor on human cells.[8] These receptors are abundantly present on human lung and small intestine epithelium, as well as the vascular endothelium. As a result of the airborne method of transmission as well as affinity for pulmonary ACE2 receptors, the infection usually presents with mild respiratory and systemic symptoms. Diagnosis at this stage includes respiratory sample PCR, serum testing for SARS-CoV-2 IgG and IgM, along with chest imaging, complete blood count (CBC) and liver function tests. CBC may reveal a lymphopenia and neutrophilia without other significant abnormalities. Treatment at this stage is primarily targeted towards symptomatic relief. Should a viable anti-viral therapy (such as remdesivir) be proven beneficial, targeting selected patients during this stage may reduce duration of symptoms, minimize contagiousness and prevent progression of severity. In patients who can keep the virus limited to this stage of COVID-19, prognosis and recovery is excellent.

### Stage II (moderate) - Pulmonary Involvement (IIa) without and (IIb) with hypoxia:

In the second stage of established pulmonary disease, viral multiplication and localized inflammation in the lung is the norm. During this stage, patients develop a viral pneumonia, with cough, fever and possibly hypoxia (defined as a $PaO_2/FiO_2$ of <300 mmHg). Imaging with chest roentgenogram or computerized tomography reveals bilateral infiltrates or ground glass opacities. Blood tests reveal increasing lymphopenia, along with transaminitis. Markers of systemic inflammation may be elevated, but not remarkably so. It is at this stage that most patients with COVID-19 would need to be hospitalized for close observation and management. Treatment would primarily consist of supportive measures and available anti-viral therapies such as remdesivir (available under compassionate and trial use). It should be noted that serum procalcitonin is low to normal in most cases of COVID-19 pneumonia. In early stage II (without significant hypoxia), the use of corticosteroids in patients with COVID-19 may be avoided.[4] However, if hypoxia ensues, it is likely that patients will progress to

requiring mechanical ventilation and in that situation, we believe that use of anti-inflammatory therapy such as with corticosteroids may be useful and can be judiciously employed. Thus, Stage II disease should be subdivided into Stage IIa (without hypoxia) and Stage IIb (with hypoxia).

### Stage III (severe) – Systemic Hyperinflammation:

A minority of COVID-19 patients will transition into the third and most severe stage of illness, which manifests as an extra-pulmonary systemic hyperinflammation syndrome. In this stage, markers of systemic inflammation appear to be elevated. COVID-19 infection results in a decrease in helper, suppressor and regulatory T cell counts.[9] Studies have shown that inflammatory cytokines and biomarkers such as interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, tumor necrosis factor-α, C-reactive protein, ferritin, and D-dimer are significantly elevated in those patients with more severe disease.[10] Troponin and N-terminal pro B-type natriuretic peptide (NT-proBNP) can also be elevated. A form akin to hemophagocytic lymphohistiocytosis (sHLH) may occur in patients in this advanced stage of disease.[11] In this stage, shock, vasoplegia, respiratory failure and even cardiopulmonary collapse are discernable. Systemic organ involvement, even myocarditis, would manifest during this stage. Tailored therapy in stage III hinges on the use of immunomodulatory agents to reduce systemic inflammation before it overwhelmingly results in multi-organ dysfunction. In this phase, use of corticosteroids may be justified in concert with the use of cytokine inhibitors such as tocilizumab (IL-6 inhibitor) or anakinra (IL-1 receptor antagonist).[11] Intravenous immune globulin (IVIG) may also play a role in modulating an immune system that is in a hyperinflammatory state. Overall, the prognosis and recovery from this critical stage of illness is poor, and rapid recognition and deployment of such therapy may have the greatest yield.

The first open-label randomized controlled clinical trial of antiviral therapy was recently reported.[3] In this study, 199 patients were randomly allocated to the antiviral agents lopinavir–ritonavir or to standard of care and this regimen was not found to be particularly effective. One reason for this may have been that the patients were enrolled during the pulmonary stage with hypoxia (stage IIb) when the viral pathogenicity may have been only one lesser dominant aspect of the overall pathophysiology, and host inflammatory responses were the predominant pathophysiology We believe that this proposed 3-stage classification system for COVID-19 illness will serve to develop a uniform scaffold to build structured therapeutic experience as healthcare systems globally are besieged by this crisis, in patients with or without transplantation.

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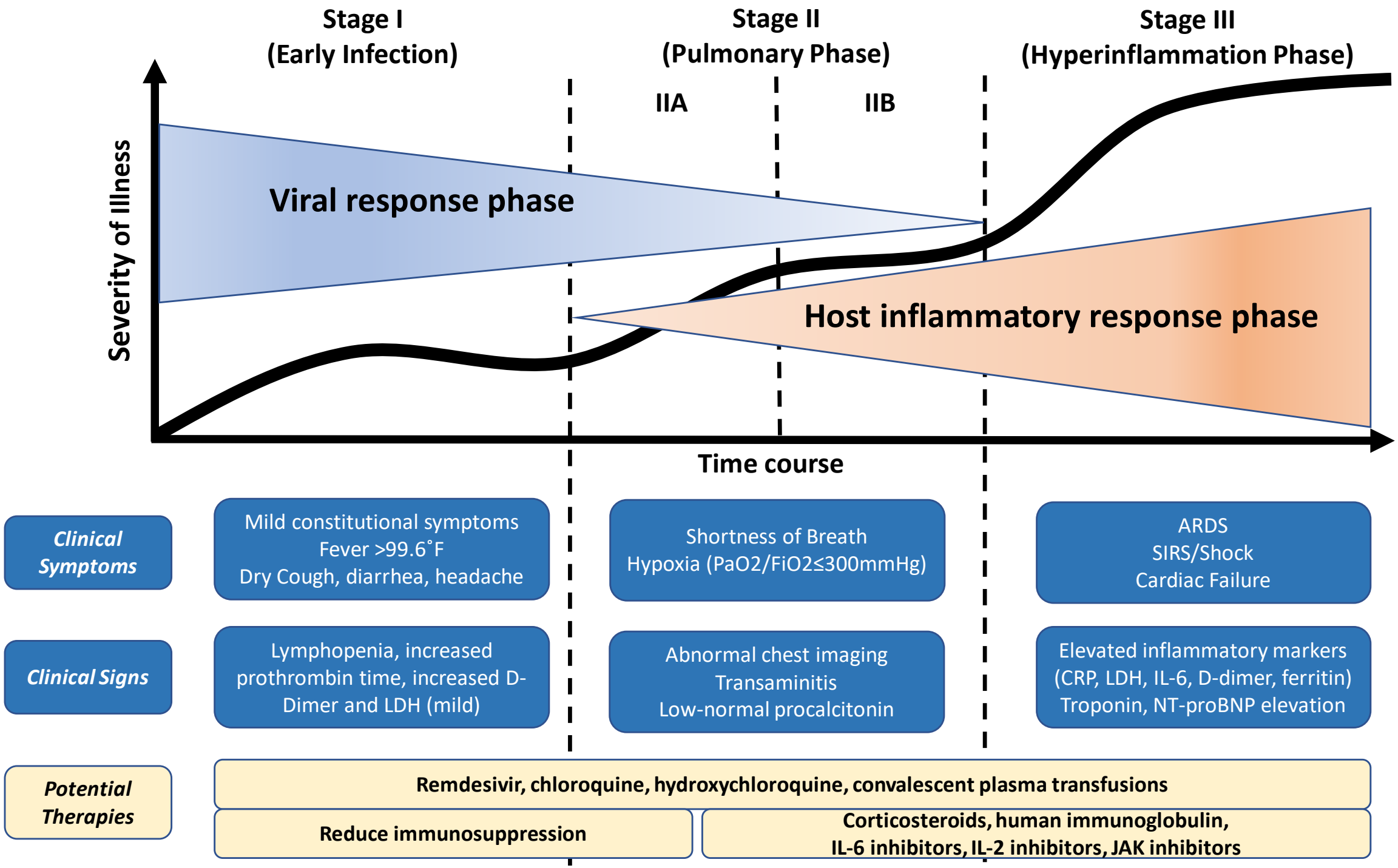
Figure 1: Classification of COVID-19 Disease States and Potential Therapeutic Targets

Legend: The figure shows 3 escalating phases of disease progression with COVID-19, with associated signs, symptoms and potential phase-specific therapies. ARDS = Acute respiratory distress syndrome; CRP = C-reactive protein; IL = Interleukin; JAK = Janus Kinase; LDH=Lactate DeHydrogenase; SIRS = Systemic inflammatory response syndrome;


Stage I
(Early Infection)
Stage II
(Pulmonary Phase)
IIA
IIB
Stage III
(Hyperinflammation Phase)
Severity of Illness
Viral response phase
Host inflammatory response phase
Time course
Clinical Symptoms
Mild constitutional symptoms
Fever >99.6˚F
Dry Cough, diarrhea, headache
Shortness of Breath
Hypoxia (PaO2/FiO2≤300mmHg)
ARDS
SIRS/Shock
Cardiac Failure
Clinical Signs
Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)
Abnormal chest imaging
Transaminitis
Low-normal procalcitonin
Elevated inflammatory markers
(CRP, LDH, IL-6, D-dimer, ferritin)
Troponin, NT-proBNP elevation
Potential Therapies
Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions
Reduce immunosuppression
Corticosteroids, human immunoglobulin,
IL-6 inhibitors, IL-2 inhibitors, JAK inhibitors