

Treatment of COVID-19 is critically phase specific

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A number of beneficial (corticosteroids and remdesivir), and potentially beneficial therapies, exist for the treatment of COVID-19. What is not widely appreciated is that patients with COVID-19 progress through several distinct phases, with each stage having a different treatment strategy (**Figure 1**). This fact is of critical importance in achieving the best possible outcomes of this disease. The symptomatic phase is marked by enormous viral replication reaching viral loads in the upper respiratory tract in excess of a billion virions per milliliter, with a very limited host inflammatory response. While patients may remain SARS-CoV-2 PCR positive for weeks (and in some cases months), active viral replication (“live” virus) does not extend after the 8th day of symptoms. (1) This critically important fact is not widely recognized. In distinction to the symptomatic phase, the pulmonary stage is characterized by a dysregulated immune response with overwhelming inflammation in response to viral fragments (“dead” non-

replicative virus). This suggests that antiviral therapies are likely to be effective *only during the symptomatic viral replicative phase*, while anti-inflammatory treatments are likely to be beneficial only during the pulmonary phase. Indeed, in the remdesivir ACTT-1 study, this agent was beneficial in patients not receiving oxygen, but was of no benefit in patients receiving high flow oxygen or mechanical ventilation (pulmonary phase). (2) Similarly, interferon may be beneficial in the early replicative phase, (3) while it was reported to be of no benefit in the pulmonary phase. (4) In contrast, in the RECOVERY trial, corticosteroids (dexamethasone) were beneficial in patients receiving oxygen and mechanical ventilation (pulmonary phase), while there was a trend towards harm in those not receiving oxygen. (5) Based on this evidence we suspect that convalescent serum and monoclonal antibodies will have limited benefit in the pulmonary phase of COVID-19.

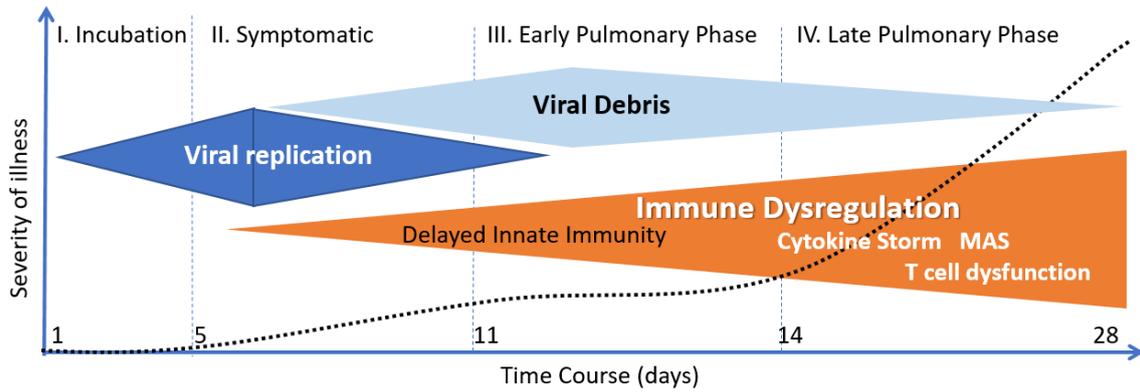
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Figure 1. Phases of COVID-19 infection



	Time Course (days)			
	1 - 5	5 - 11	11 - 14	14 - 28
Ground-glass infiltrates		+	++	+++ ++++
Clinical Symptoms	Fever, malaise, cough, headache, diarrhea	SOB – Mild hypoxia ≤4 L/min N/C & aSat < 94%		Progressive hypoxia
Treatment approach	Antiviral Rx	Anti-inflammatory Rx		
Potential therapies	? Ivermectin	Methylprednisolone 40mg q 12 inc. to 80 mg q 12 if reqd.		
	? Interferon-α	Enoxaparin 60 mg/day	Enoxaparin 1mg/kg s/c q 12	
	Remdesivir (IV)			

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