COVID-19 Therapeutic Trials Must Encompass More Diverse Interventions and Targets in Disease Course

OBJECTIVE: A vaccine for SARS-CoV-2 is not likely to be validated for efficacy and safety for 12 to 18 months, making it especially important to develop a robust pathologic understanding and balanced clinical trials pipeline. Media coverage of the pandemic has resulted in grossly uneven perception of therapeutic efficacy, focusing the public's attention on headline-grabbing claims (for example, hydroxychloroquine) that do not necessarily correlate with sound representative exploration of the most promising drug candidates. It is important to ensure that clinical trials of COVID-19 therapies align with data-supported goals by targeting the most clinically promising approaches at the appropriate point in the disease course. This review will examine how well COVID-19 treatment research comports with current clinical needs.

METHODS: We have created a pathophysiological flow chart that includes theorized physiological mechanisms based on clinical observation along the COVID-19 disease course. The chart shows which drug and clinical support interventions are implemented at which points along the disease time course. We selected three primary classifications--antivirals, immunomodulators, and supportive treatments--as representative, though not exhaustive, of commonly used therapies for COVID-19. We then provide an overview of a sampling of clinical trials currently being conducted for these categories comprising ~19% of total ongoing COVID-19 trials listed on clinicaltrial.gov, comparing them to the chart in order to determine how well they are aligned.

RESULTS and DISCUSSION: Our survey revealed a heavy clustering of resources around high-profile drug candidates as well as a mismatch between the timing of therapeutic interventions and the potential high-impact points along the disease course. In this analysis, we call out a few, specific compounds that receive disproportionate attention relative to other potential interventions. HCQ (49 trials, more than 3 times the number of any other compound in our analysis), Lopinavir + Ritonavir (12), Tocilizumab (12), and Remdesivir (9), exemplify the lopsided attention in therapeutic study. In contrast, we note that there are currently only two clinical trials for ivermectin as a potentially potent antiviral, despite very strong in-vitro inhibition and a tolerable safety profile. Meanwhile, there are no current trials investigating, for example, pulmonary vasodilators or inhaled steroids with antiviral properties (ciclesonide) for respiratory support. Researchers have identified as many as 69 FDA approved compounds in trials for another indication, or in preclinical stage, that have shown strong *in vitro* activity against COVID-19 for which there are no current clinical trials.

In order to assess where in the disease process clinical trials are focused, trials were grouped using the patient severity designations of mild (outpatient), moderate (hospitalized), and severe (in ICU or near ICU). We discovered that nearly all trials focus on late stage, hospitalized patients. Of the 123 specific trial arms we reviewed, 60% focused on moderate and 36% focused on severe disease, with only 4% addressing outpatient disease. Of all the compounds we reviewed, only hydroxychloroquine (HCQ) is being studied at the outpatient stage (10% of surveyed HCQ trials). To further illustrate the current emphasis of therapeutic trials at later stages in the disease process, trials were also delineated by drug class. For immunomodulators (21 trials), 43% focused on moderate and 57% focused on severe disease, where both antiviral (42) and supportive care (11) have 64% of trials focused on moderate and 36% focused on severe disease stages, respectively. While most antiviral trials currently focus on more progressive disease, very early administration may be required in order to achieve adequate viral load reduction. Furthermore, given the skewed age distribution of mortality, trials may benefit from delineating low-risk and high-risk subgroups by age and comorbidity prior to randomization.

With increased understanding of the natural history and pathophysiology of the virus, we emphasize that clinical trials should target phenotypic variations in disease presentation. As cases progress, multiple patterns of morbidity are emerging. For example, while a hypercoagulable state is a common feature of septic ARDS, localized microthrombotic phenomena have been reported to occur in earlier disease states. With respect to lung pathophysiology, COVID-19 appears to diverge into what is known as "Type H" and "Type L" phenotypes. Type H is similar to "classic" ARDS and is characterized by hypoxia and hyperinflammation, possibly with elevated pulmonary artery pressure and right-heart failure. Type L is characterized by a loss of perfusion regulation rather than reduced lung capacity and may occur sooner in the disease progression and be amenable to earlier intervention. However, for the compounds we reviewed, only 4 clinical trials are investigating supportive care in severe cases of Type L, with limited therapeutic diversity (3 of 4 trials are studying the treatment of nitric oxide). Drugs such as PDE-5 inhibitors, acetazolamide, and nifedipine may be especially useful in preventing and treating Type L, or in preventing the progression of Type L to Type H. However because there are not more drugs included in current clinical trials, clinicians will not have data to guide them in how best to treat these patients.

CONCLUSION: Resources for COVID-19 treatment research appear to be suboptimally and disproportionately directed, and would benefit from an organized clinical trials scaffold to rapidly test multiple repurposed compounds along a matrix of risk, disease phase, and specific pathologic presentation. Currently, nearly all clinical trials focus on hospitalized patients, making it difficult to discern the benefit of early treatment and runs the risk of prematurely discarding medications that could prove useful at earlier disease timepoints. Lopsided media attention has resulted in numerous trials on very few therapies while other promising compounds are not studied at all, resulting in an undiversified pipeline that is not well-hedged against possible failure. Research funding should expand its focus to prioritize investigations of early stage disease and compounds for which we currently lack trial data.

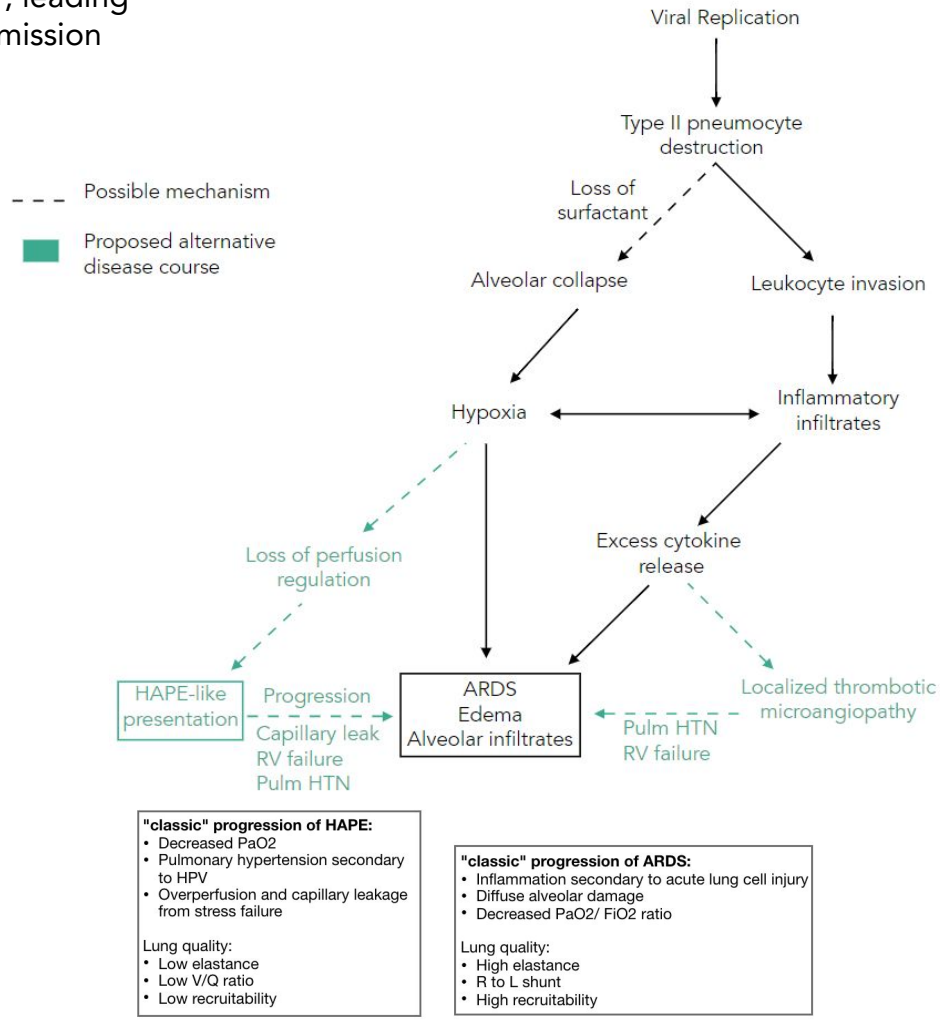
A proposed pathophysiological disease pathway for COVID-19, leading to the two most commonly seen phenotypes upon hospital admission

Figure 1. SARS-CoV-2, once introduced to the body in sufficient quantities, migrates to the lungs and enters type II pneumocytes (surfactant producing cells) via the ACE2 surface receptor. The virus quickly hijacks cellular machinery for replication and eventually induces cell lysis in order to release viral progeny.

Following the leftmost pathway, destruction of these cells may lead to a loss of pulmonary surfactant production and alveolar collapse due to the resulting increase in local surface tension. Alveolar damage reduces the overall gas-exchange surface area and decreases the partial pressure of oxygen in the blood. To compensate, the lungs begin selectively constricting capillaries around damaged alveoli and redirecting blood to yet undamaged regions, resulting in pulmonary hypertension. In this scenario, indicated by the box in the lower left, a patient may present with symptoms similar to "high altitude sickness", and depending on their innate hypoxic ventilatory drive, they may be experiencing some amount of respiratory distress or could appear comfortable at even very low SpO2 values. Progression from this status involves dependent pulmonary hypertension resulting in capillary leakage from stress failure, manifesting as edema/ alveolar infiltrates and eventually leading to, complicating, or accelerating classic acute respiratory distress syndrome (ARDS) from the widespread inflammation (shown in the lower right box).

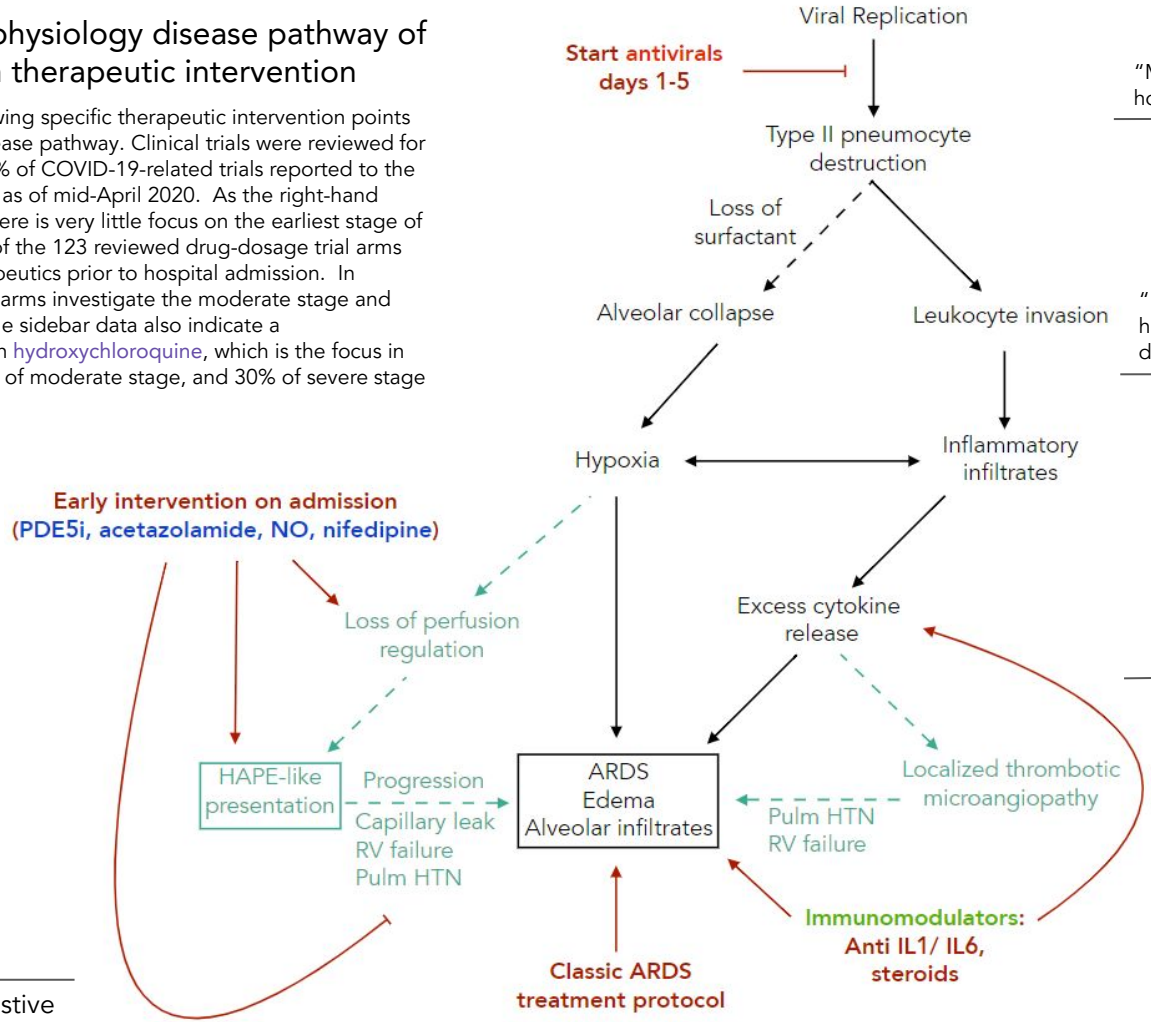
Following the rightmost, primarily immune-mediated pathway, viral progeny are released from inoculated pneumocytes and infect nearby cells, resulting in leukocyte recruitment to the area under attack. The ensuing inflammatory response draws increasing quantities of immune cells to the damaged alveoli by way of capillary dilation, enabling them to "spill" their contents around the affected alveoli. The consequences are two-fold, first exacerbating hypoxia due to loss of gas-exchange surface as described above, and then culminating in excessive cytokine release via a runaway positive feedback loop. The latter is characteristic of a hyperactive immune response and swiftly advances the acute alveolar injury to full acute respiratory distress syndrome.

Recent pathology reports suggest that there may also be an underappreciated component of localized thrombotic microangiopathy (bottom right) in the lungs contributing to elevated pulmonary artery pressures and high frequency of right-heart failure in COVID-19 mortality. Formation of these microthrombi may also lead to respiratory disease progression and development of ARDS.



Proposed pathophysiology disease pathway of SARS-CoV-2 with therapeutic intervention

Figure 2. Schematic showing specific therapeutic intervention points along the COVID-19 disease pathway. Clinical trials were reviewed for 10 drugs, comprising 19% of COVID-19-related trials reported to the database clinicaltrial.gov as of mid-April 2020. As the right-hand sidebar demonstrates, there is very little focus on the earliest stage of the disease, with only 5 of the 123 reviewed drug-dosage trial arms (4%) administering therapeutics prior to hospital admission. In contrast, 60% of the trial arms investigate the moderate stage and 36% the severe stage. The sidebar data also indicate a disproportionate focus on hydroxychloroquine, which is the focus in 100% of mild stage, 42% of moderate stage, and 30% of severe stage antiviral trial arms.



# of Trials at each disease stage

"Mild," pre hospitalization, day 1-3

- Hydroxychloroquine: 5
- Antivirals: 0
- Immunomodulators: 0
- Supportive care: 0

"Moderate," at hospital admission, day 4-7

- Hydroxychloroquine: 31
- Antivirals: 27
- Immunomodulators: 9
- Supportive care: 7

"Severe," late stage, day 7+

- Hydroxychloroquine: 13
- Antivirals: 15
- Immunomodulators: 12
- Supportive care: 4

Illustrative, not exhaustive

**Trial data retrieved as of 4/13/20

Antivirals

Pathologic process	Drug	Class	Mechanism	# of trials	Pre/Post Prophylaxis	Mild	Moderate	Severe
RNA virus reproduces itself in host via RNA-dependent RNA polymerase enzyme	HCQ	Antimalarial	Exact mech unknown; raises pH of organelles, reduces inflammatory response	49	19	5	31	13
	Remdesivir	Antiviral	Adenosine analogue; targets RNA polymerase	9	0	0	7	7
	Lopinavir + Ritonavir	Antiviral	Protease inhibitors acting against the viral 3CL protease	12	2	0	10	8
	Favipiravir	Antiviral	Targets RNA-dependent RNA polymerase (RdRp) enzymes, which are necessary for the transcription and replication of viral genomes.	8	0	0	10	0

- # of trials represents the total number of clinical trials referenced, and is not equivalent to the sum of trials for each patient severity type
- Source: Clinicaltrials.gov & Covid 19 Trials Tracker, mild = outpatient, moderate = hospitalized, severe = ICU or near-ICU
- Trial data retrieved as of 4/13/20

Illustrative, not exhaustive

Immunomodulators

Pathologic process	Drug	Class	Mechanism	# of trials	Pre/Post Prophylaxis	Mild	Moderate	Severe
In response to viral infection, hyperinflammation due to excessive cytokines (interferons, interleukins, chemokines, CSFs, TNRs)	Tocilizumab	Immunomodulator	Antibody blocking against the interleukin-6 RECEPTOR (IL-6R). Does not interfere with IL-6 production directly (may reduce it by negative feedback, but unclear).	12	0	0	7	11
	Baricitinib	Immunomodulator	Reversibly Inhibits JAK (janus kinase; thereby interfering with the JAK-STAT signaling pathway) by blocking JAK1 and JAK2	2	0	0	2	1

- # of trials represents the total number of clinical trials referenced, and is not equivalent to the sum of trials for each patient severity type
- Source: Clinicaltrials.gov & Covid 19 Trials Tracker, mild = outpatient, moderate = hospitalized, severe = ICU or near-ICU
- Trial data retrieved as of 4/13/20

Illustrative, not exhaustive

Supportive Treatment

Pathologic process	Drug	Class	Mechanism	# of trials	Pre/Post Prophylaxis	Mild	Moderate	Severe
Hypoxia, pulmonary vasoconstriction	Nitric Oxide NO	Supportive Care | Hypoxia	Vasodilator, decreases hypoxemia	6	0	0	5	3
	Sildenafil/ Tadalafil	Supportive Care | Hypoxia	Pulmonary artery vasodilation, inhibit vascular remodeling	1	0	0	2	1
	Acetazolamide	Supportive Care | Hypoxia	carbonic anhydrase inhibitor, acidifies blood, stimulates deeper breathing	N/A	0	0	0	0
	Nifedipine	Supportive Care | Hypoxia	Ca++ channel blocker, peripheral arterial vasodilator	N/A	0	0	0	0

- # of trials represents the total number of clinical trials referenced, and is not equivalent to the sum of trials for each patient severity type
- Source: Clinicaltrials.gov & Covid 19 Trials Tracker, mild = outpatient, moderate = hospitalized, severe = ICU or near-ICU
- Trial data retrieved as of 4/13/20

Illustrative, not exhaustive

References

1. The DataLab and Centre for Evidence-Based Medicine (CEBM), University of Oxford. Covid-19 TrialsTracker. http://covid19.trialstracker.net/index.html. Accessed April 4, 2020.

2. Fox SE, Akmatbekov A, et al. Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series from New Orleans. 2020. https://www.medrxiv.org/content/10.1101/2020.04.06.20050575v1.full.pdf

3. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, Camporota L. COVID-19 pneumonia: different respiratory treatment for different Phenotypes? *Inten Care Med*. 2020. DOI: 10.1007/s00134-020-06033-2. https://www.esicm.org/wp-content/uploads/2020/04/684_author-proof.pdf

4. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. *Am J Resp Crit Care Med*. 2020. DOI: 10.1164/rccm.202003-0817LE. https://www.atsjournals.org/doi/10.1164/rccm.202003-0817LE

5. Gonçalves A, Bertrand J, Ke R, et al. Timing of antiviral treatment initiation is critical to reduce SARS-Cov-2 viral load. April 7, 2020. DOI: 10.1101/2020.04.04.20047886. https://www.medrxiv.org/content/10.1101/2020.04.04.20047886v1

6. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug Repurposing. 2020. DOI: https://doi.org/10.1101/2020.03.22.002386. https://www.biorxiv.org/content/10.1101/2020.03.22.002386v1.full.pdf

7. Mark N. Twitter thread on HPV and HVD. *Threadreader*. April 6, 2020. https://threadreaderapp.com/thread/1247332371218628609.html#

8. Solaimanzadeh I. Acetazolamide, Nifedipine and Phosphodiesterase Inhibitors: Rationale for Their Utilization as Adjunctive Countermeasures in the Treatment of Coronavirus Disease 2019 (COVID-19). *Cureus*. 2020;12(3):e7343. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7096066/#REF25

9. Sufang T, Weidong Hu, Li Niu, Huan Liu, Haibo Xu, Shu Yuan Xiao. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. Journal of Thoracic Oncology. 2020. DOI:https://doi.org/10.1016/j.jtho.2020.02.010. https://www.jto.org/article/S1556-0864(20)30132-5/fulltext

10. US National Library of Medicine, National Institutes of Health. ClinicalTrials.gov database. https://clinicaltrials.gov/. Accessed April 14, 2020.

11. Worcester S. Is Protocol-Driven COVID-19 Ventilation Doing More Harm Than Good? *Medscape*. April 6, 2020. https://www.medscape.com/viewarticle/928236

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