COVID-19 Updates: May 18, 2020

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TREATMENT

EPIDEMIOLOGY

INFECTION CONTROL

DIAGNOSIS

DISEASE

CDC: Childcare Center Recommendations

- States/Tribes determine closures – dependent on level of community transmission
  - Closed, except programs serving essential/emergency workers – Oregon
  - Open, (some with reduced group size and add'l sanitation required) –Washington, Wyoming, Idaho, Minnesota, Montana, Alaska, Arizona, California, New Mexico, Oklahoma
- Implement social distancing strategies
- Intensify cleaning and disinfection efforts
- Modify drop off and pick up procedures
- Implement screening procedures up arrival
- Maintain an adequate ratio of staff to children
  - Substitute caregivers who can fill in if your staff members are sick or stay home to care for sick family members.
- Staff members and older children should wear face coverings within the facility, when possible (NOT babies or children under age two)

https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/guidance-for-childcare.html

Update:
Multisystem Inflammatory Syndrome in Children (MIS-C)

- As of May 12, 2020, the New York State Department of Health identified 102 patients (and investigating more)
- It is currently unknown if this multisystem inflammatory syndrome is specific to children or if it also occurs in adults
- Healthcare providers who have cared or are caring for patients younger than 21 years of age meeting MIS-C criteria should report suspected cases to their local, state, or territorial health department

https://emergency.cdc.gov/han/2020/han00432.asp

Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged <21 years presenting with fever[i], laboratory evidence of inflammation[ii], and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

[i]Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
[ii]Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

Additional comments

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

https://emergency.cdc.gov/han/2020/han00432.asp

WHO Case Definition MIS-C

Children and adolescents 0–19 years of age with fever ≥ 3 days

AND two of the following:

1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
2. Hypotension or shock.
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

AND

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

Evidence of COVID-19 **(**RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19

American Society of Health-System Pharmacists evidence assessment

ashp

Assessment of Evidence for COVID-19-Related Treatments: Updated 5/15/2020

The information contained in this evidence table is emerging and rapidly evolving because of ongoing research and is subject to the professional judgment and interpretation of the practitioner due to the uniqueness of each medical facility's approach to the care of patients with COVID-19 and the needs of individual patients. ASHP provides this evidence table to help practitioners better understand current approaches related to treatment and care. ASHP has made reasonable efforts to ensure the accuracy and appropriateness of the information presented. However, any reader of this information is advised ASHP is not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the evidence table in any and all practice settings. Any reader of this document is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this evidence table and will bear no responsibility or liability for the results or consequences of its use. Public access to AHFS Drug Information® (https://www.ahfsdi.com/login) is currently available with the username "ahfs@ashp.org" and password "covid-19." ASHP's patient medication information is available at http://www.patientmedication.com/.

Select entries were updated on 5/15/2020; these can be identified by the date that appears in the Drug(s) column.

TABLE OF CONTENTS

ANTIVIRAL AGENTS

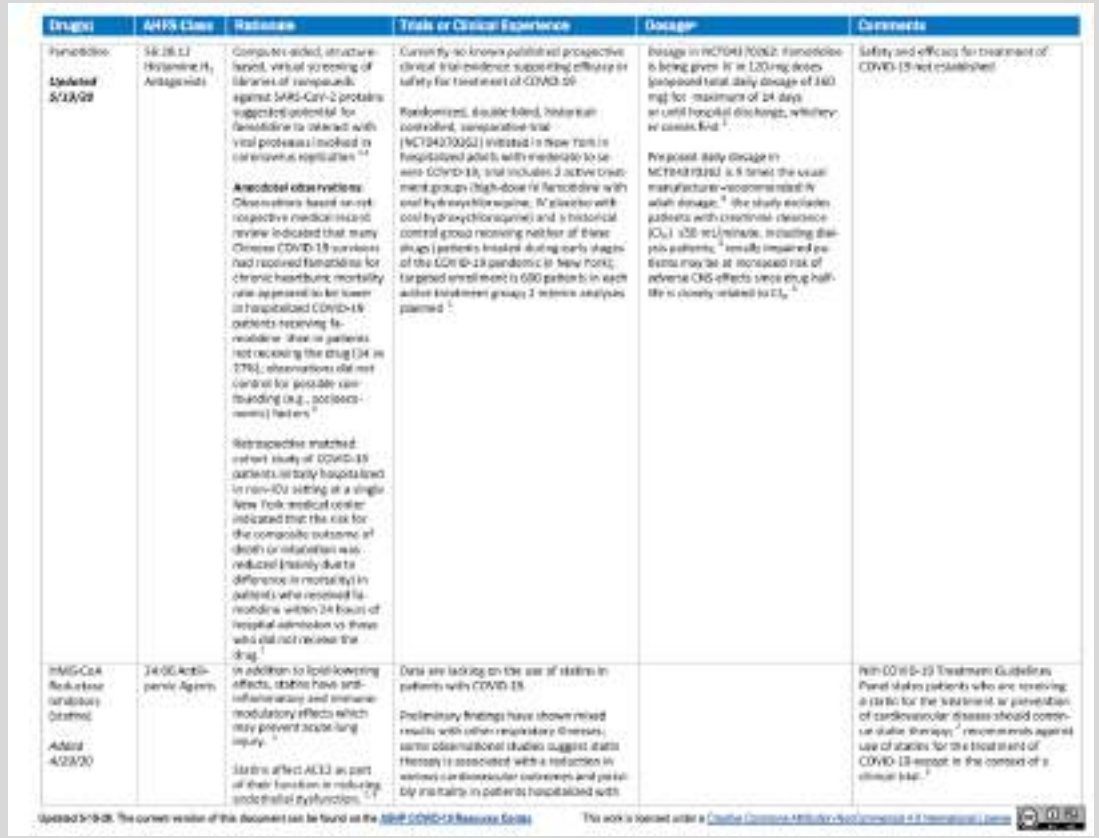
- BALOXAVIR
- CHLOROQUINE PHOSPHATE
- FAVIPIRAVIR (Avigan®, Areplenir)
- HIV PROTEASE INHIBITORS (e.g., LPV/RTV, Kaletra®)
- HYDROXYCHLOROQUINE (Plaquenil®)
- NEURAMINIDASE INHIBITORS (e.g., oseltamivir)
- UPDATED • REMDESIVIR
- UMIFENOVIR (Arbidol®)

SUPPORTING AGENTS

- ANAKINRA
- ASCORBIC ACID
- AZITHROMYCIN
- UPDATED • BARICITINIB (Olumiant®)
- COLCHICINE
- CORTICOSTEROIDS (general)
- COVID-19 CONVALESCENT PLASMA
- EPOPROSTENOL (Inhaled)
- METHYLPREDNISOLONE (DEPO-Medrol®, SOLU-Medrol®)
- NITRIC OXIDE (inhaled)
- NOREPINEPHRINE (Levophed®)
- SARILUMAB (Kevzara®)
- SILTUXIMAB (Sylvant®)
- UBROGEPANT (Ubrelvy®)
- TOCILIZUMAB (Actemra®)

OTHER

- ACE INHIBITORS, ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)
- ANTICOAGULANTS (low-molecular-weight heparin [LMWH], unfractionated heparin [UFH])
- UPDATED • FAMOTIDINE
- HMG-CoA REDUCTASE INHIBITORS (statins)
- IMMUNE GLOBULIN (IGIV, IVIG, polyvalent)
- UPDATED • IVERMECTIN
- NEBULIZED DRUGS
- NICLOSAMIDE
- NITAZOXANIDE
- NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDs)
- TISSUE PLASMINOGEN ACTIVATOR (t-PA; alteplase)



Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage*	Comments
Famotidine **Updated 5/13/20**	56:28.12 Histamine H_2 Antagonists	Computer-aided, structure-based, virtual screening of libraries of compounds against SARS-CoV-2 proteins suggested potential for famotidine to interact with viral proteases involved in coronavirus replication.[1,2] **Anecdotal observations:** Observations based on retrospective medical record review indicated that many Chinese COVID-19 survivors had received famotidine for chronic heartburn; mortality rate appeared to be lower in hospitalized COVID-19 patients receiving famotidine (four or patients not receiving the drug [34 vs 276]; observations did not control for possible confounding (e.g., psoriasis-severity) factors.[3] Retrospective matched cohort study of COVID-19 patients initially hospitalized in non-ICU setting at a single New York medical center indicated that the risk for the composite outcome of death or intubation was reduced (mainly due to difference in mortality) in patients who received famotidine within 24 hours of hospital admission vs those who did not receive the drug.[4]	Currently no known published prospective clinical trial evidence supporting efficacy or safety for treatment of COVID-19. Randomized, double-blind, historical-controlled, comparative trial (NCT04370002) initiated in New York in hospitalized adults with moderate to severe COVID-19; trial includes 3 active treatment groups (high-dose IV famotidine with oral hydroxychloroquine, IV placebo with oral hydroxychloroquine) and a historical control group receiving neither of these drugs; patients treated during early stages of the COVID-19 pandemic in New York); targeted enrollment is 600 patients in each active treatment group; 3 interim analyses planned.[5]	Dosage in NCT04370002: famotidine is being given IV in 120-mg doses (proposed total daily dosage of 360 mg) for maximum of 14 days or until hospital discharge, whichever comes first.[5] Proposed daily dosage in NCT04370002 is 6 times the usual manufacturer-recommended IV adult dosage;[6] the study excludes patients with creatinine clearance (CL_{cr}) ≤30 mL/minute, including dialysis patients;[5] renally impaired patients may be at increased risk of adverse CNS effects since drug half-life is closely related to CL_{cr}.[6]	Safety and efficacy for treatment of COVID-19 not established
HMG-CoA Reductase Inhibitors (statins) *Added 4/23/20*	24:06 Antihyperlipidemic Agents	In addition to lipid-lowering effects, statins have anti-inflammatory and immune-modulatory effects which may prevent acute lung injury.[7] Statins affect ACE2 as part of their function in reducing endothelial dysfunction.[7,8]	Data are lacking on the use of statins in patients with COVID-19. Preliminary findings have shown mixed results with other respiratory diseases; some observational studies suggest statin therapy is associated with a reduction in various cardiovascular outcomes and possibly mortality in patients hospitalized with		With COVID-19 Treatment Guidelines Panel states patients who are receiving a statin for the treatment or prevention of cardiovascular disease should continue statin therapy;[7] recommends against use of statins for the treatment of COVID-19 except in the context of a clinical trial.[7]

Updated 5-15-20. The current version of this document can be found on the ASHP COVID-19 Resource Center. This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table

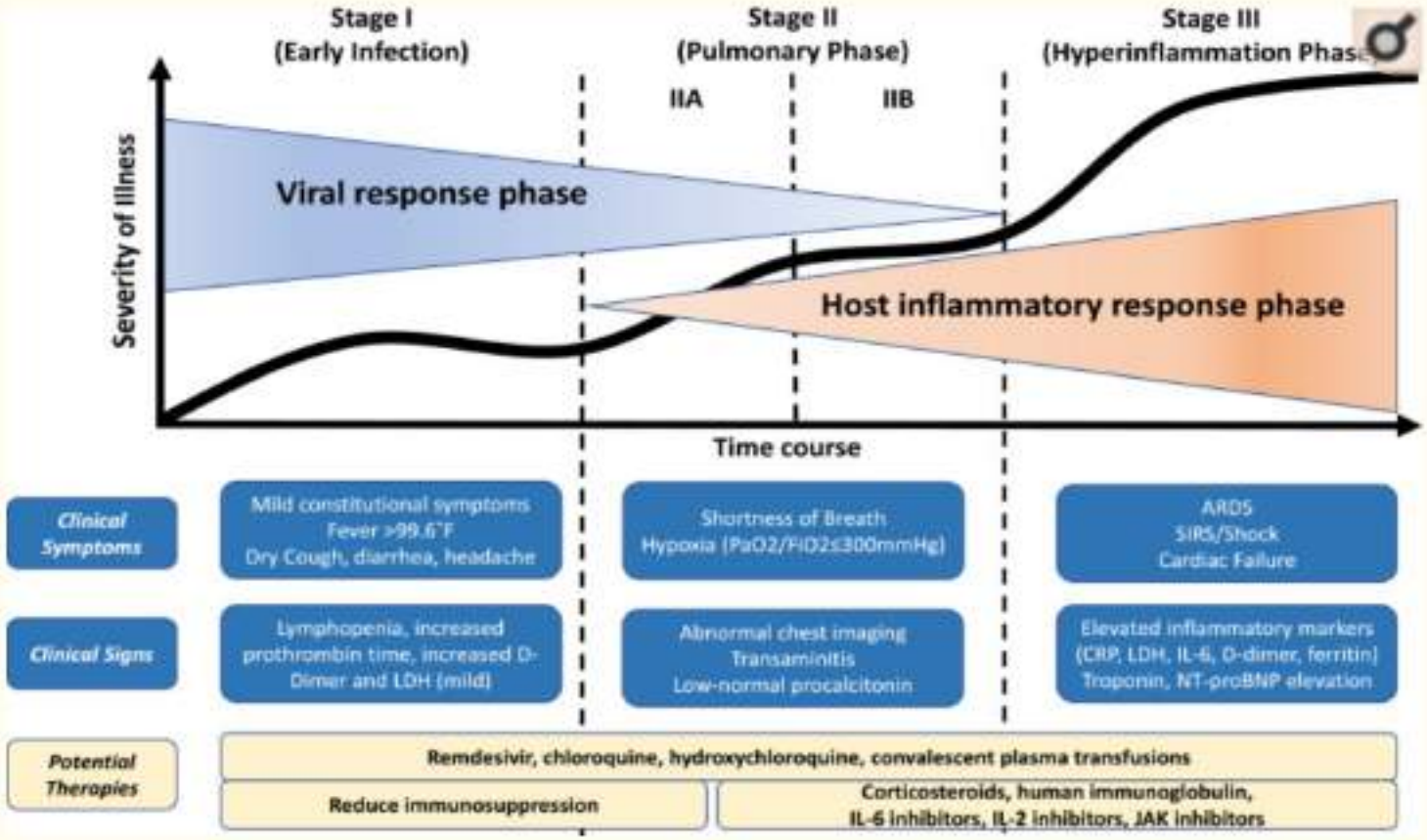


Figure 1

Classification of COVID-19 Disease States and Potential Therapeutic Targets

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.

COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal

Siddiqui H, Mehra M.

Journal of Heart and Lung Transplantation March 2020

Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomized, phase 2 trial

- *Hospitalized adults (n=127) with mild symptoms were assigned to:*
  - Lopinavir – ritonavir/ ribavirin/ interferon β-1b (14 days) **OR**
  - Lopinavir – ritonavir "control" group.
- *Using intention-to-treat analysis, the triple therapy group:*
  - Achieved a negative nasopharyngeal swab in less time (7 days) than the control group (12 days)
  - Had more rapid resolution of symptoms and shorter hospital stays

The Lancet: Published online May 8, 2020 https://doi.org/10.1016/S0140-6736(20)31042-4

Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study

- **Retrospective cohort** 29 COVID-19 patients with moderate-to-severe symptoms were given high-dose intravenous anakinra and compared with 16 patients who weren't given anakinra
- **Inclusion criteria**
  - Consecutive patients age ≥18 years) with COVID-19 with moderate-to-severe was defined as
    - Acute-onset respiratory failure with bilateral infiltrates on chest radiography or CT
    - Hypoxaemia [PaO2:FiO2] ≤200 mm Hg with a positive end-expiratory pressure [PEEP]
  - Hyperinflammation (defined as serum C-reactive protein ≥100 mg/L, ferritin ≥900 ng/mL, or both)
  - Managed with non-invasive ventilation outside of the ICU and who received standard treatment of 200 mg hydroxychloroquine twice a day orally and 400 mg lopinavir with 100 mg ritonavir twice a day orally.
- **Compared** to a retrospective cohort of 16 similar patients who did not receive anakinra

www.thelancet.com/rheumatology **Published online May 7, 2020 https://doi.org/10.1016/S2665-9913(20)30129-6**

Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study

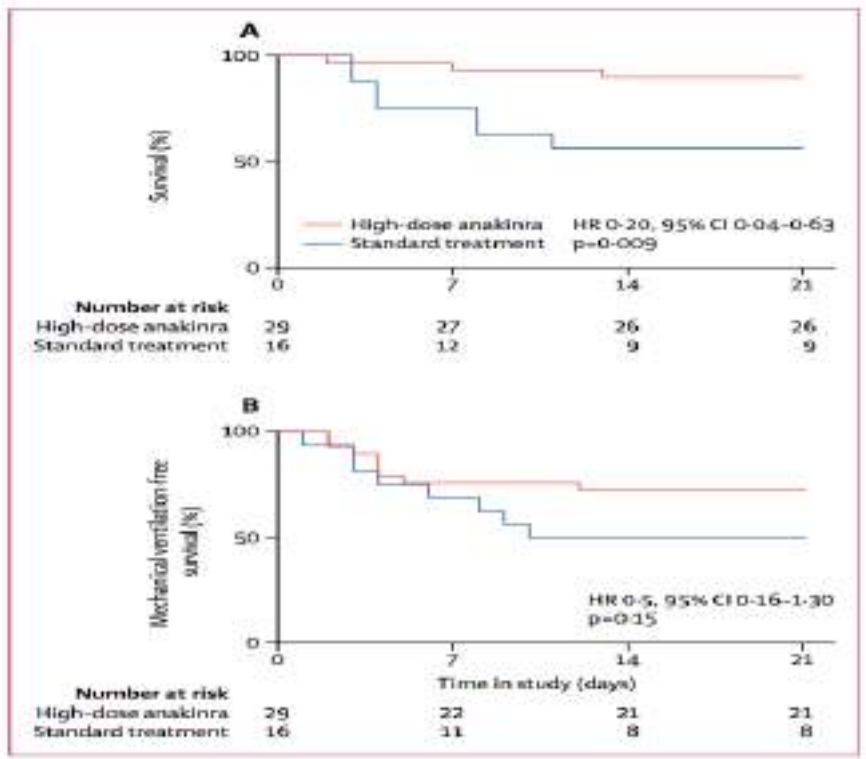


Figure 1: **Survival and mechanical ventilation-free survival at 21 days**
Plots show survival (A) and mechanical ventilation-free survival (B) at 21 days of patients with COVID-19, ARDS, and hyperinflammation managed outside the intensive care unit with CPAP and high-dose anakinra (n=29) or receiving CPAP and standard treatment only (n=16). For mechanical ventilation-free survival (B), death and mechanical ventilation were considered equivalent to treatment failure. COVID-19=coronavirus disease 2019. ARDS=acute respiratory distress syndrome. CPAP=continuous positive airway pressure. HR=hazard ratio.

- In this retrospective cohort study of patients with COVID-19 and ARDS managed with non-invasive ventilation outside of the ICU, treatment with high-dose anakinra was safe and associated with clinical improvement in 72% of patients. Confirmation of efficacy will require controlled trials.

www.thelancet.com/rheumatology **Published online May 7, 2020 https://doi.org/10.1016/S2665-9913(20)30129-6**

COVID-19: HYDROXY CHLOROQUINE

- Outcome comparison of 1400 consecutive patients in New York with COVID-19 outcomes between those who received hydroxychloroquine and those who did not
- Multivariable risk adjustment for age, gender, comorbidities and medications
- The primary end point was a composite of intubation or death in a time-to-event analysis.
- Outcomes were compared in patients who received hydroxychloroquine with those in patients who did not, using a multivariable Cox model with inverse probability weighting according to the propensity score.

Geleris J, et al Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19 published on May 7, 2020, at NEJM.org

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

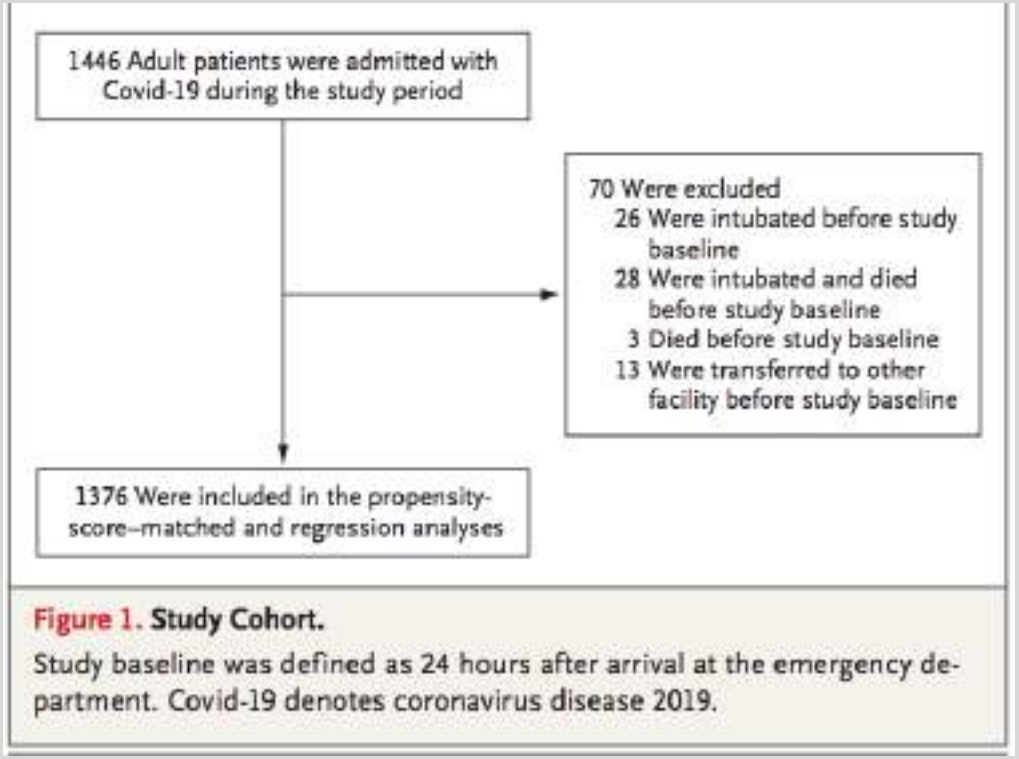
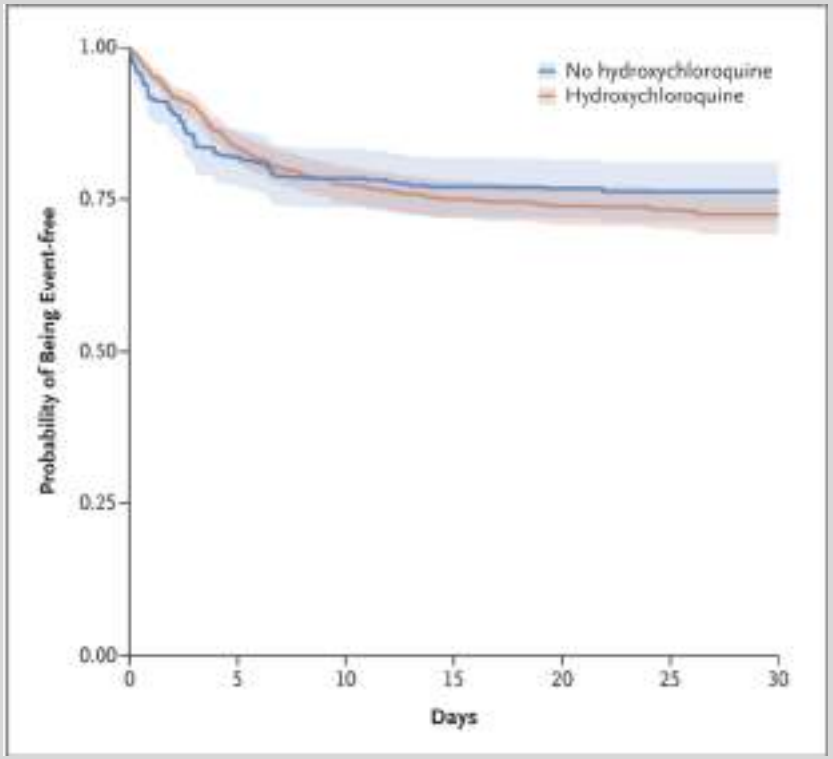


Figure 1. Study Cohort.

Study baseline was defined as 24 hours after arrival at the emergency department. Covid-19 denotes coronavirus disease 2019.



No association of HCQ use with reduced risk for intubation or death

Geleris J, et al published on May 7, 2020, at NEJM.org

Thrombosis and Thromboembolism Prophylaxis

- Elevated d-dimer and thrombosis have been reported as part of the acute illness spectrum of Covid-19
- A prospective series of 184 patients with proven Covid-19 admitted to Dutch ICUs found that
  - 31% had thrombotic complications (27% VTE and 3.7% arterial thrombosis) despite DVT prophylaxis
- Multicenter observational series described 2,773 nonrandomized COVID-19 patients hospitalized in New York who had undocumented and likely variable indications for anticoagulation.
  - No significant association between anticoagulation and in-hospital survival overall
  - However, for the 395 patients who required mechanical ventilation, in-hospital mortality was 29.1% for those treated with anticoagulation and 62.7% in patients who did not receive anticoagulation.

Journal of American College of Cardiology. https://doi.org/10.1016/j.jacc.2020.05.001
ACP Clinical update

COVID-19 and Thrombosis

Case series of 11 COVID-19 Autopsies

- 58% had deep venous thrombosis on autopsy
- In 4 cases, cause of death massive PE with the thrombi originating in the deep veins of the lower limbs
- 3 additional cases had fresh DVT in both legs and no pulmonary embolism
- High incidence of thromboembolic events suggests an important role of COVID-19-induced coagulopathy

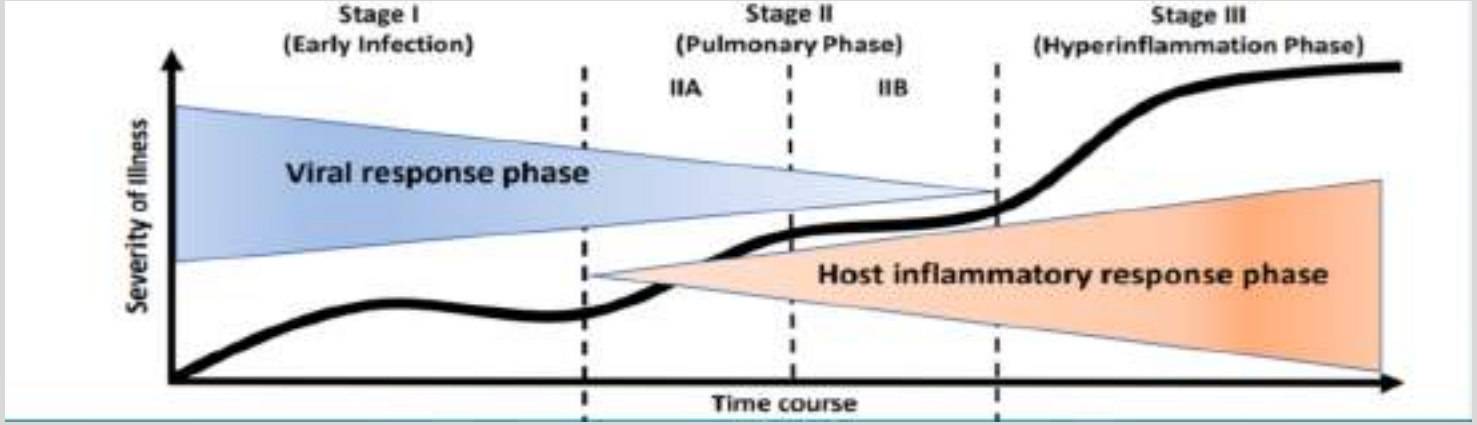
Wichmann D, Sperhake J, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Ann Intern Med. 2020; [Epub ahead of print 6 May 2020]

COVID-19: Prolonged aPTT

- In UK, 200 patients with severe COVID-19, 20% had a prolonged activated partial-thromboplastin time (aPTT)
  - Lupus anticoagulant assays positive in 91% of these patient
- None of these patients had clinically significant bleeding
- Clinicians should not withhold use of anticoagulants for thrombosis while awaiting further investigation of a prolonged aPTT, nor should they withhold thrombolytic therapy in the face of a high-risk pulmonary embolism on the basis of a prolonged aPTT alone

Bowles L et al Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with Covid-19 NEJM May 5, 2020

Considerations for Treatment: Timing?



Antiviral Treatments

Remdesivir

Convalescent Plasma

Anti-inflammatory Treatments

Prophylactic Anticoagulation

Full Anticoagulation