

COVID-19 Updates: May 22, 2020

Jorge Mera, MD, FACP
Whitney Essex, MSN, FNP-BC
Cherokee Nation Health Services

TREATMENT

EPIDEMIOLOGY

INFECTION CONTROL

DIAGNOSIS

DISEASE

American Society of Health-System Pharmacists evidence assessment



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.ahfscdi.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.safemedication.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®, Favilavir)
- [HIV PROTEASE INHIBITORS](#) (e.g., LPV/RTV, Kaletra®)
- [HYDROXYCHLOROQUINE](#) (Plaquenil®)
- [NEURAMINIDASE INHIBITORS](#) (e.g., oseltamivir)
- UPDATED • [REMEDSIVIR](#)
- [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)
- [RUXOLITINIB](#) (Jakafi®)
- [SARILUMAB](#) (Kefzara®)
- [SILTUXIMAB](#) (Sylvant®)
- [SIROLIMUS](#) (Rapamune®)
- [TOCILIZUMAB](#) (Actemra®)

OTHER

- [ACE INHIBITORS, ANGIOTENSIN II RECEPTOR BLOCKERS \(ARBs\)](#)
- [ANTICOAGULANTS](#) (low molecular weight heparin [LMWH], unfractionated heparin [UFH])
- [FAMOTIDINE](#)
- [HMG-CoA REDUCTASE INHIBITORS](#) (statins)
- [IMMUNE GLOBULIN](#) (IGIV, IVIG, γ-globulin)
- 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 ¹⁻⁴ 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 than in patients not receiving the drug (14 vs 27%); observations did not control for possible confounding (e.g., socioeconomic) factors ⁵ 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 ⁷	Currently no known published prospective clinical trial evidence supporting efficacy or safety for treatment of COVID-19 Randomized, double-blind, historical-controlled, comparative trial (NCT04370262) initiated in New York in hospitalized adults with moderate to severe COVID-19; trial includes 2 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; 2 interim analyses planned ³	Dosage in NCT04370262: 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 ³ Proposed daily dosage in NCT04370262 is 9 times the usual manufacturer-recommended IV adult dosage; ⁶ the study excludes patients with creatinine clearance (Cl _{cr}) ≤50 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 4/29/20	24:06 Antilipemic Agents	In addition to lipid-lowering effects, statins have anti-inflammatory and immunomodulatory effects which may prevent acute lung injury. ¹ Statins affect ACE2 as part of their function in reducing endothelial dysfunction. ^{2,4}	Data are lacking on the use of statins in patients with COVID-19. Preliminary findings have shown mixed results with other respiratory illnesses; some observational studies suggest statin therapy is associated with a reduction in various cardiovascular outcomes and possibly mortality in patients hospitalized with		NIH COVID-19 Treatment Guidelines Panel states patients who are receiving a statin for the treatment or prevention of cardiovascular disease should continue statin therapy; ² recommends against use of statins for the treatment of COVID-19 except in the context of a clinical trial. ²

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](#)



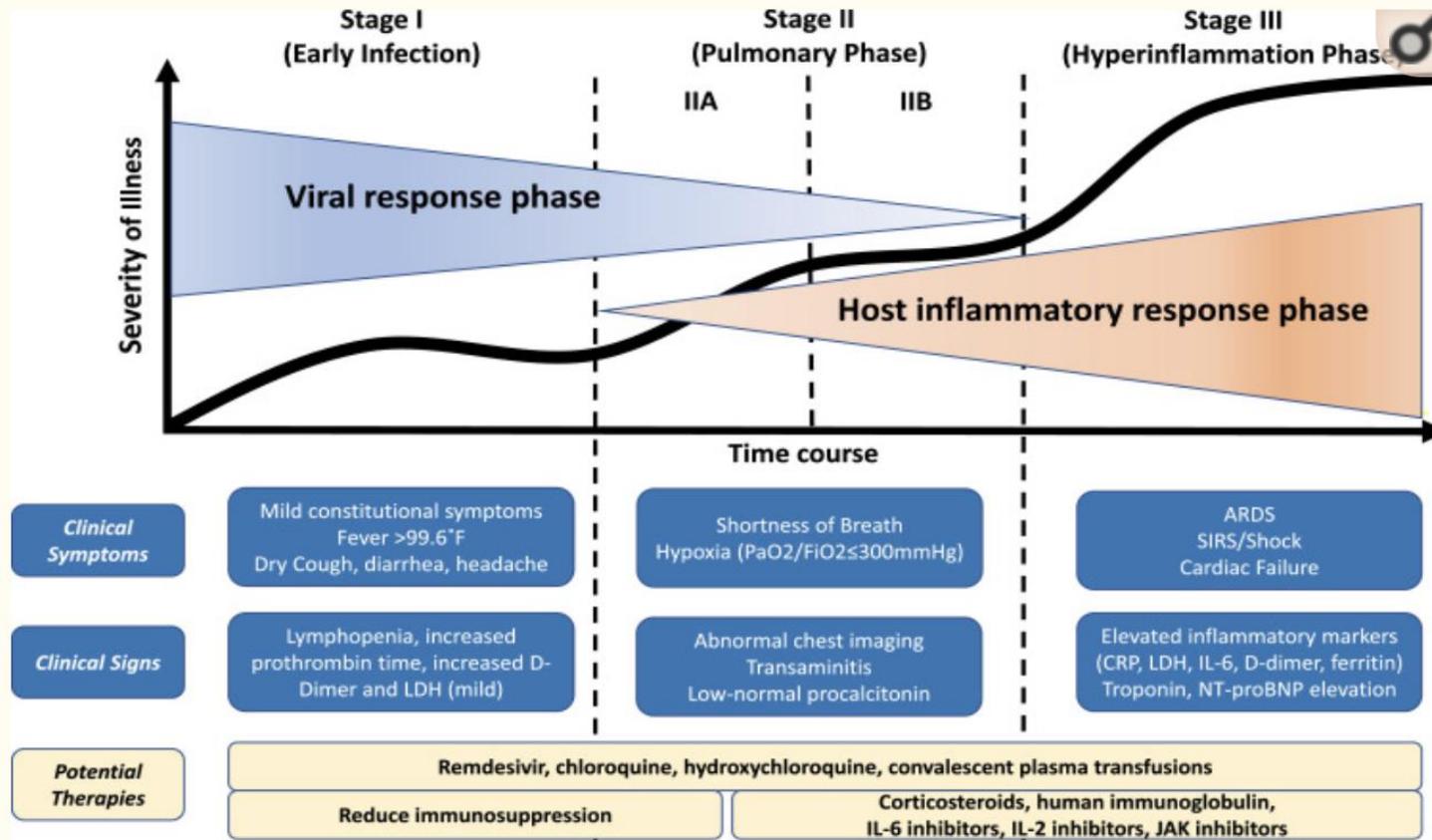


Figure 1

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

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 were given high-dose intravenous anakinra and compared with 16 patients who weren't given anakinra
- **Inclusion criteria**
 - Age ≥ 18 years) with COVID-19
 - Moderate-to-severe ARDS
 - 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

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

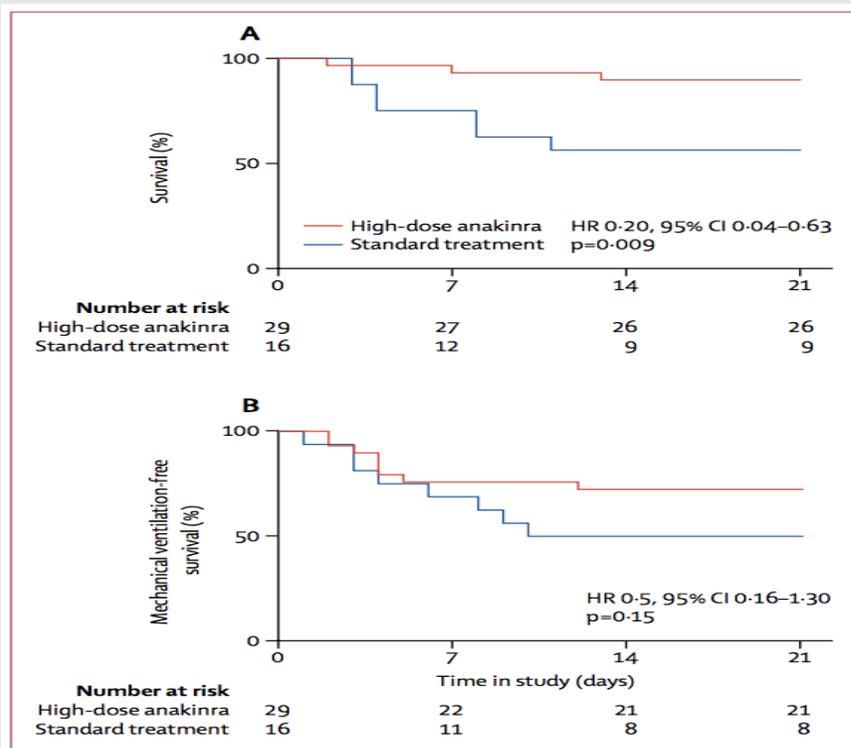


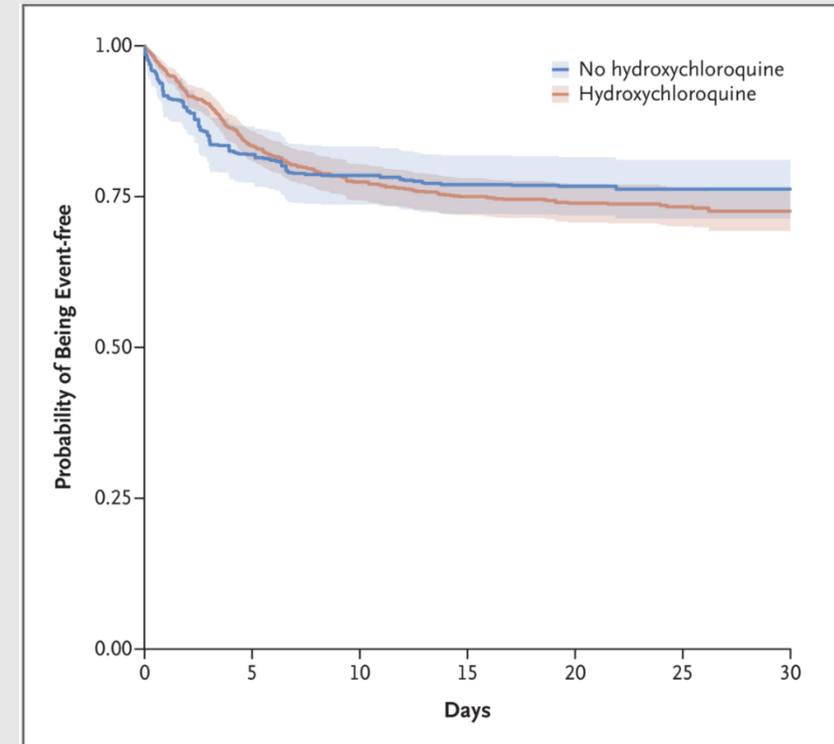
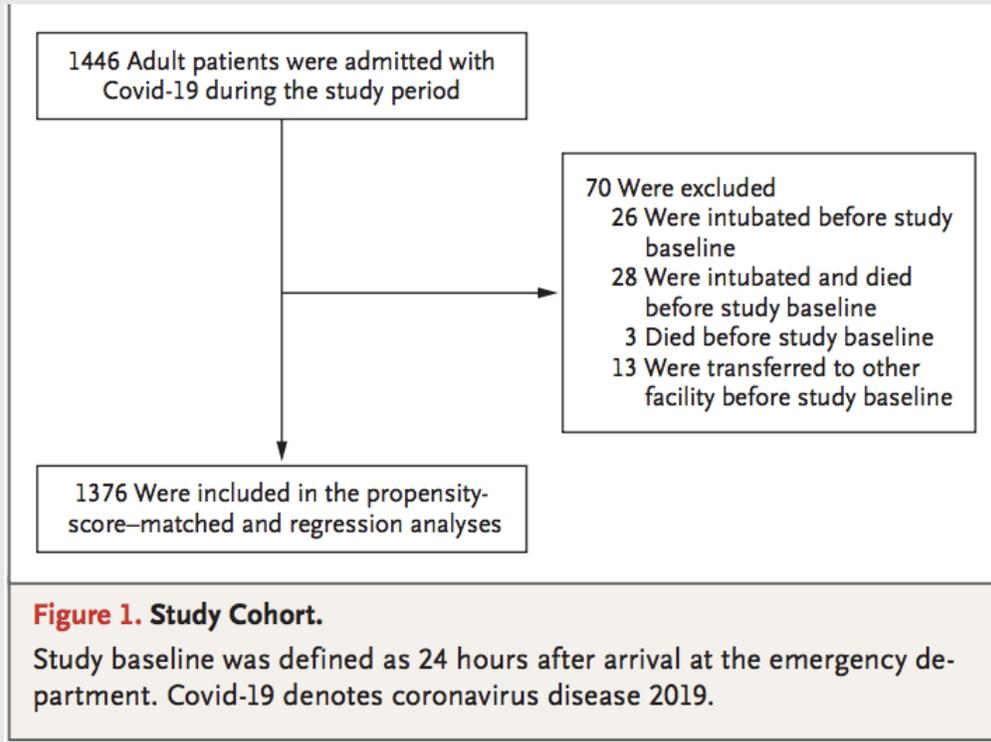
Figure 1: Survival and mechanical ventilation-free survival at 21 days
Plots show survival (A) and mechanical ventilation-free survival (B) at 21 days of patients with COVID-19, ARDS, and hyperinflammation managed outside the intensive care unit with CPAP and high-dose anakinra (n=29) or receiving CPAP 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.

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.

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19



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

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 standard dose thromboprophylaxis
 - In an autopsy series of 11 deceased patients with COVID-19, the majority of whom were treated with thromboprophylaxis, thrombosis of small and mid-sized pulmonary arteries was found in all 11 patients.
- 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.

COVID-19 and Thrombosis

Case series of 12 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
- Many of these patients did not receive chemoprophylaxis for thrombosis

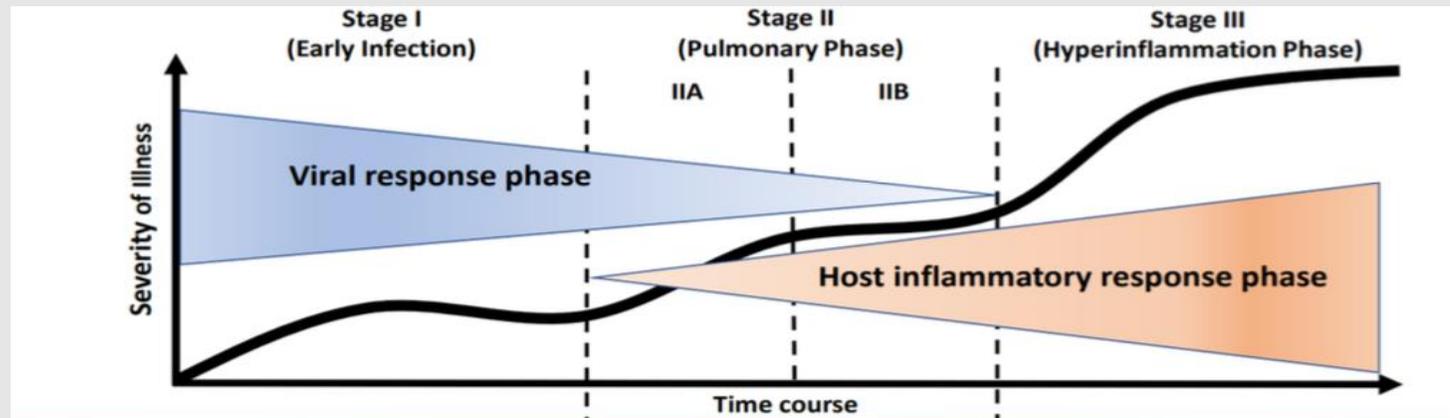
Wichmann D, Sperhake J, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. *Ann Intern Med.* 2020; [Epub ahead of print 6 May 2020]

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

Howes Q, 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

COVID-19 and Cats

Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus

- SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks, but ferrets and cats are permissive to infection.
- Cats are susceptible to airborne infection.

Shi J, Wen Z, Zhong G et al. Science 2020 Apr 8 doi: 10.1126/science.abb7015



Transmission of SARS-CoV-2 in Domestic Cats

- Three domestic cats were inoculated with SARS-CoV-2 and cohoused with 3 other non infected cats.
- Five 5 days later, virus was detected in all three cats that were cohoused with the inoculated
- Given the need to stop the coronavirus disease 2019 pandemic through various mechanisms, including breaking transmission chains, a better understanding of the role cats may play in the transmission of SARS-CoV-2 to humans is needed.

NEJM May 13, 2020 DOI: 10.1056/NEJMc2013400

COVID-19 and Household Animals (HHA)

- **People with COVID-19 and in home isolation should be advised to restrict interaction with HHA**
 - A person with *symptomatic COVID-19* should maintain separation from HHA as they would with other household members
 - Avoid direct contact, including petting, snuggling, being kissed or licked, sleeping in the same location, and sharing food or bedding.
 - If possible, a household member should be designated to care for pets and should follow standard hand washing
 - In accordance with the Americans with Disabilities Act, service animals should be permitted to remain with their handlers.
- **HHA may require alternative care or re-homing if the owner is unable to care for them or has surrendered them**
 - A home receiving a new HHA should follow standard hand washing practices before and after interacting with the animal.
 - Shelters receiving HHA should ensure they review and adhere to their established biosafety and biosecurity practices

COVID-19 and Household Animals (HHA)

Pet Telemedicine



Care for HHA that are sick or injured should be coordinated with the household's local veterinarian

- The owner should call ahead and arrange the hospital or clinic visit
- Telemedicine may also be appropriate
- Veterinarians that see animals with a new, concerning illness that could be compatible with SARS-CoV-2 should contact their state public health veterinarian for guidance regarding testing.

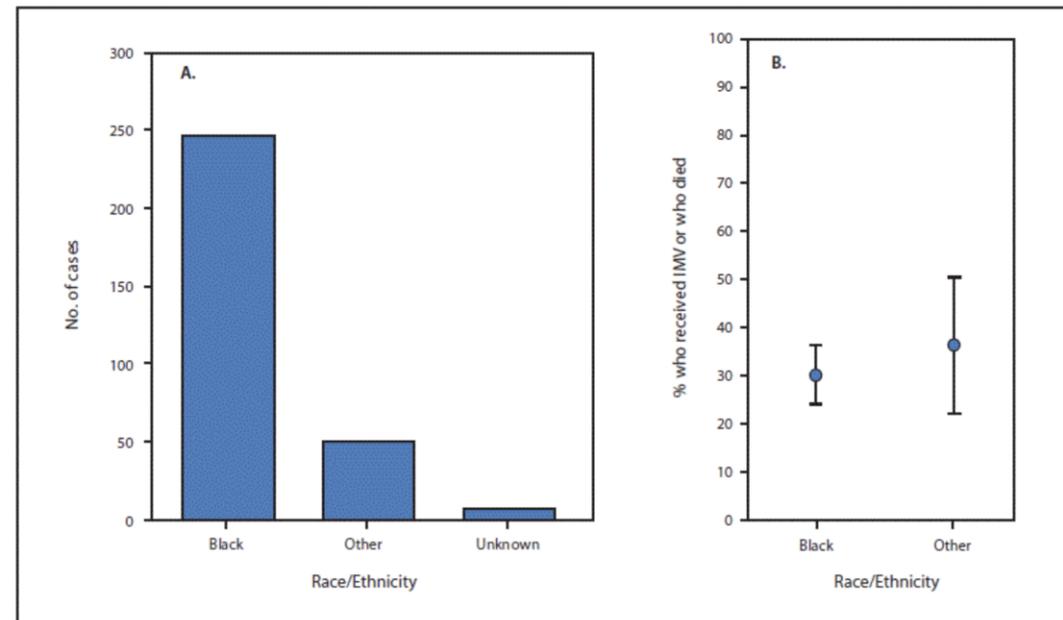
CDC.gov

Characteristics and clinical outcomes of adult patients hospitalized with COVID-19, Georgia, March 2020

- Median age 60 years
- Patients age <65 years: in 62%
- Non-Hispanic Black: 83%
- Patients without underlying risk conditions: 26%
- Admitted to ICU: 39%

In this cohort black patients were overrepresented, and their clinical outcomes were similar to those of nonblack patients. One in four hospitalized patients had no recognized risk factors for severe COVID-19.

FIGURE 2. Number of hospitalized patients with COVID-19 (N = 305)* (A) and percentage who received or died (B),[†] by race/ethnicity[§] — eight hospitals, Georgia, March 2020



Abbreviations: COVID-19 = coronavirus disease 2019; IMV = invasive mechanical ventilation.

* A total of 273 patients had available race/ethnicity data and known hospitalization outcomes.

[†] Vertical bars represent 95% confidence intervals for proportions.

[§] Black was defined as non-Hispanic black race/ethnicity; other includes all other racial/ethnic groups.

Epidemiology of and Risk Factors for Coronavirus Infection in Health Care Workers: A Living Rapid Review.

Ann Intern Med. 2020 May 05

- Studies included: **64**
 - Studies that addressed burden of HCW infections: **43** (15 on SARS-CoV-2)
 - Studies that addressed risk factors: **34** (3 on SARS-CoV-2).
- **Health care workers accounted for a significant proportion of coronavirus infections** and may experience particularly high infection incidence after unprotected exposures, but illness severity was lower than in non-HCWs.
- **Depression, anxiety, and psychological distress were common** in HCWs during the COVID-19 outbreak.
- **The strongest evidence on risk factors was on PPE use and decreased infection risk.**
 - The association was most consistent for masks but was also observed for gloves, gowns, eye protection, and hand washing;
 - Evidence suggested a dose-response relationship.
 - No study evaluated PPE reuse.
 - Exposures involving intubations, direct patient contact, contact with bodily secretions were associated with increased risk
 - Infection control training was associated with decreased risk.

Table 1. Exposure History and Risk for Infection With SARS-CoV-2, SARS-CoV-1, or MERS-CoV in HCWs*

Author, Year (Reference)	Intubation	Directness of Contact	Oxygen Administration and Related Exposures	Number or Duration of Contacts and Proximity to Patient	Other Exposures
SARS-CoV-2					
Ran et al, 2020 (61)	Endotracheal tube removal: RR, 0.63 (95% CI, 0.06-7.08)	-	-	-	CPR: RR, 0.63 (95% CI, 0.06-7.08) Fiberoptic bronchoscopy: RR, 0.63 (95% CI, 0.06-7.08)

Table 2. Mask Use and Risk for Infection With SARS-CoV-2, SARS-CoV-1, or MERS-CoV in HCWs*

Author, Year (Reference)	Mask Use Versus Nonuse	Comparison of Mask Types	Consistency of Mask Use	Multiple Mask Layers Versus Single Layer
SARS-CoV-2				
Wang et al, 2020 (70)	In department with N95 mask use (yes vs. no): <i>OR, 0.04 (95% CI, 0.002-0.61)†; adjusted OR, 0.002 (95% CI, 0-0.21)</i> (note: reversed from no vs. yes as reported in study, for which the 95% CI, was 97.73-∞)	-	-	-

Table 3. Infection Prevention and Control Factors (Other Than Masks) and Risk for Infection With SARS-CoV-2, SARS-CoV-1, or MERS-CoV in HCWs*

Study, Year (Reference)	Gown	Glove	Handwashing	Eye Protection	PPE
SARS-CoV-2					
Wang et al, 2020 (70)	-	-	-	-	-
Ran et al, 2020 (61)	-	-	Unqualified handwashing: <i>RR, 2.64 (95% CI, 1.04-6.71)</i> Suboptimal handwashing before patient contact: <i>RR, 3.10 (95% CI, 1.43-6.73)</i> Suboptimal handwashing after patient contact: <i>RR, 2.43 (95% CI, 1.34-4.39)</i>	-	Improper PPE: <i>RR, 2.82 (95% CI, 1.11-7.18)</i>

COVID-19: VIRUS IN SEMEN

- SARS-CoV-2 has been detected in the semen of men with COVID-19
- 6 out of 38 men with confirmed illness in China who provided a semen sample for tested positive for the virus
- Out of these 6 - 4 were in the acute stage of infection and 2 were in the recovery phase
- It is not yet known whether the virus can be transmitted sexually