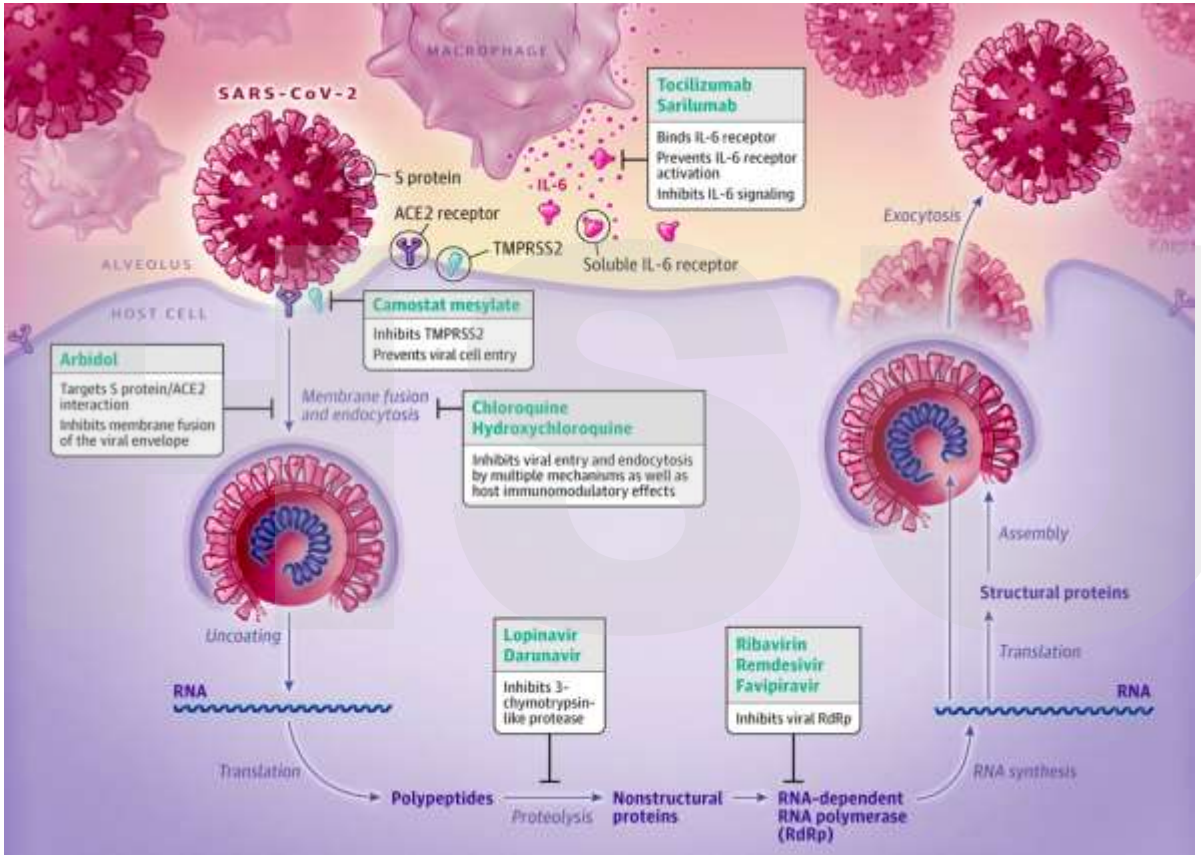
Treatment Options for COVID-19

June 3, 2020 Ellie Sukerman, MD

Objectives

- Review pharmacologic therapies available and/or under investigation for COVID-19
- How to access select medications
- Guidance on concomitant medications

Quick Virology Overview



Sanders, et al. *JAMA.* 2020.

Repurposed and Experimental Agents

Image: https://www.nature.com/articles/d41591-020-00019-9

Therapy by Disease Severity

- Mild COVID-19 -> symptomatic treatment
- Moderate and severe COVID-19 -> consider therapy

https://www.who.int/publications-detail/clinical-management-of-covid-19. Accessed 6/1/20.

NIH Treatment Guidelines Summary

- Do not recommend the use of any agents for pre- or post-exposure prophylaxis outside a clinical trial
- No specific treatment recommended for persons with suspected or confirmed asymptomatic or pre-symptomatic infection
- Currently, no drug has been proven to be safe and effective for treating COVID19. Insufficient data to recommend either for or against the use of any antiviral or immunomodulatory agent

https://covid19treatmentguidelines.nih.gov/introduction/. Accessed 5/30/20.

What's old is new again…

- Hydroxychloroquine (HCQ), Chloroquine (CQ)
- Lopinavir/ritonavir (LPV/r)
- Ribavirin
- Umifenovir (Arbidol)
- Nitazoxanide
- Ivermectin

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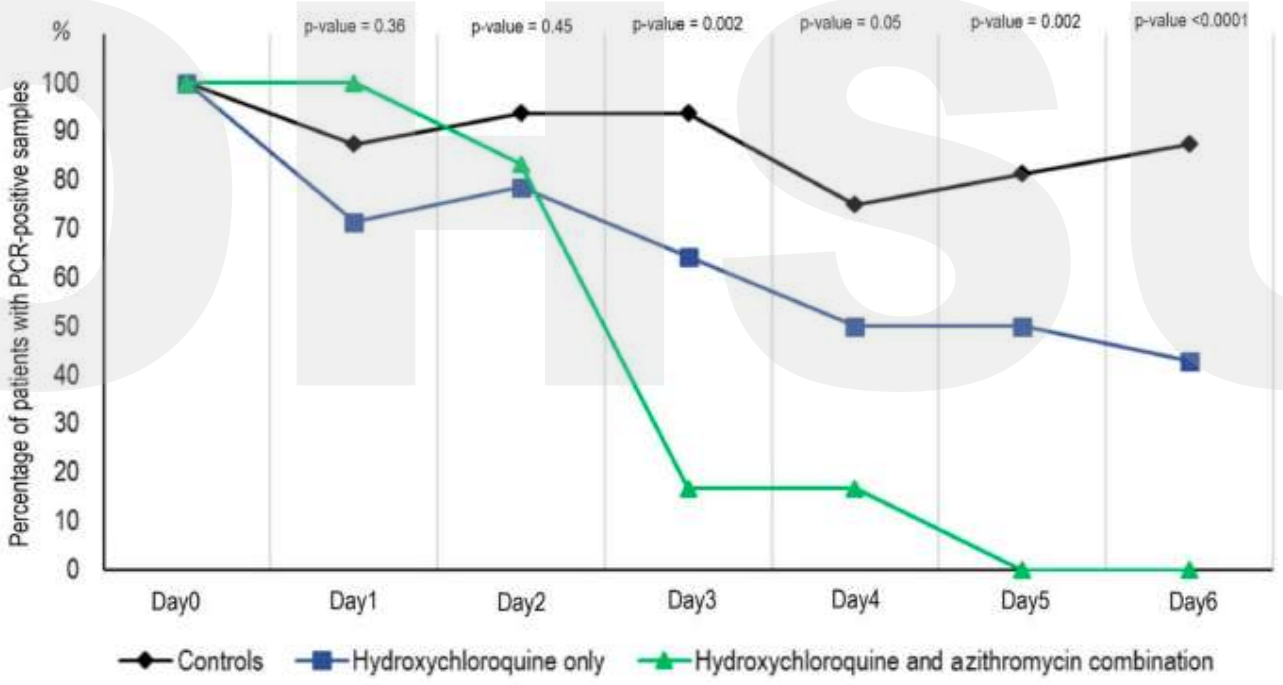
HCQ

- *In vitro* activity against SARS-CoV-2
- Relatively well tolerated but can cause serious adverse effects (e.g., QTc prolongation, ventricular arrhythmia, retinopathy, hypoglycemia)
- Initial publications reported positive results but data limited by study design, study design flaws, small numbers

Yao, et al. *Clin Infect Dis.* 2020. Gautret, et al. *Int J Antimicrob Agents.* 2020:105949. Million M, et al. *Travel Med Infect Dis.* 2020:101738.

HCQ +/- azithromycin

- Gautret, *et al.* – open-label, non-randomized trial



Gautret, et al.. *Int J Antimicrob Agents.* 2020:105949.

HCQ + azithromycin

- Gautret, *et al.* - pilot observational study
  - Uncontrolled, non-comparative, observational study in cohort of 80 inpatients treated with HCQ and azithromycin x min. 3d
- Million, *et al.* – retrospective analysis
  - 1061 inpatients treated with same regimen for min. 3d
- Both studies lack a comparator group

Gautret, et al. *Travel Med Infect Dis.* 2020;34:101663. Million, et al. *Travel Med Infect Dis.* 2020:101738.

HCQ +/- azithromycin

- **Preprint Magagnoli, *et al.*** – HCQ in US VA
  - Retrospective cohort study of hospitalized pts
  - HCQ +/- azithromycin did not improve mortality or reduce need for mechanical ventilation
  - Tx with HCQ alone associated with an increased risk of mortality compared to standard care

- **Geleris, *et al.* NEJM.** – observational study
  - No significant association between HCQ use and primary composite endpoint of intubation or death

Geleris J, Sun Y, Platt J, et al. *N Engl J Med.* 2020.

Mehra, *et al.* - Lancet

- Multinational registry analysis
  - No evidence of benefit of HCQ or CQ alone or in combination with a macrolide for in-hospital mortality
  - Data suggests tx is independently associated with increased risk of in-hospital mortality and de-novo ventricular arrhythmia

Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet.* 2020.

THE CORONAVIRUS CRISIS

WHO Halts Hydroxychloroquine Trial Over Safety Concerns

May 25, 2020 · 4:34 PM ET

THE CORONAVIRUS CRISIS

France Bars Use Of Hydroxychloroquine In COVID-19 Cases

May 27, 2020 · 12:39 PM ET

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Scientists Question Validity of Major Hydroxychloroquine Study

Experts are demanding verification of data and methods used in a study of malaria drugs used to treat Covid-19. The study suggested the drugs may have increased deaths.

The drug hydroxychloroquine, touted by President Donald Trump and others in recent months as a possible treatment for people infected with the Covid-19. George Frey/Reuters

https://zenodo.org/record/3862789#.XtMpvi3MyfX. Accessed 5/30/20.

Guidelines for CQ/HCQ

- No high-quality evidence for efficacy of CQ/HCQ +/- azithromycin
- Guidelines recommend use only within context of a clinical trial or cite insufficient evidence to recommend for or against
- FDA cautions against use outside of a hospital setting or clinical trial given risk of dysrhythmias
- NIH recommends AGAINST high-dose CQ (600mg BID x 10d)

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 5/23/20.
https://covid19treatmentguidelines.nih.gov/antiviral-therapy/chloroquine-or-hydroxychloroquine/. Accessed 5/23/20.

Lopinavir/ritonavir (LPV/r)

- NIH recommends **against** LPV/r or other HIV protease inhibitors except in context of a clinical trial
- In vitro activity against SARS but poor selectivity -> high levels of drug needed to achieve therapeutic levels, not likely to be tolerable, drug-drug interactions are a concern
- Cao, *et al*. NEJM. LPV/r vs. standard care failed to find clinical or virologic benefit (pts enrolled median 13d after sx onset)

Cao B, Wang Y, Wen D, et al. *N Engl J Med.* 2020;382(19):1787-1799.

Ribavirin

- In vitro activity against SARS limited and required high concentrations to inhibit viral replication
- Studies in SARS either inconclusive or demonstrated possible harm
  - Dose-dependent hematologic toxicity
  - Hepatic toxicity

Sanders, et al. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA.* 2020.

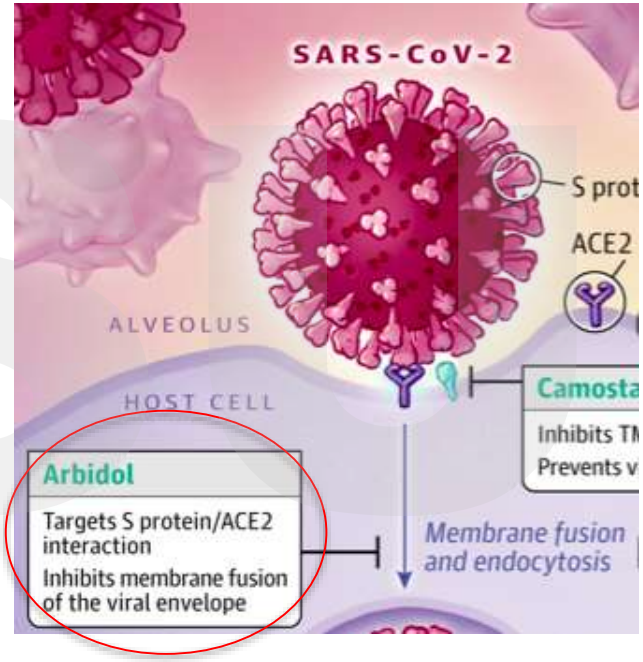
Combo therapy – Hung, *et al.*

- Phase II RCT
  - Interferon B-1b* + LPV/r + ribavirin vs. LPV/r
    - Interferon only given to pts enrolled <7d after sx onset
  - No serious adverse events in combination group
  - Combo therapy associated with significant reduction in time to negative PCR, sx alleviation and LOS in pts started on tx <7d after sx onset

Hung IF, Lung KC, Tso EY, et al. *Lancet.* 2020.

Umifenovir (Arbidol)

- Targets S protein/ACE2 interaction, inhibits membrane fusion of viral envelope
- In vitro data suggests activity against SARS and SARS-CoV-2
- Limited clinical data in COVID-19 – efficacy not established
- RCTs ongoing



Lian, et al. *Clin Microbiol Infect.* 2020.
Wang, et al. *Cell Discov.* 2020;6:28.
Wang, et al. *Clin Infect Dis.* 2020.

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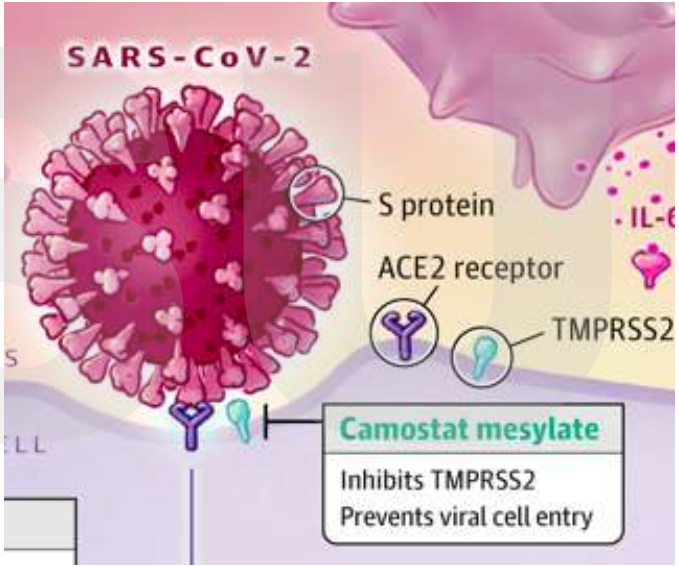
Nafamostat and Camostat

- Camostat found in vitro to block viral entry of SARS-CoV-2
- Preprint report that nafamostat may block viral entry in vitro more efficiently than camostat
- Clinical trials ongoing



Hoffmann, et al. *Cell.* 2020;181(2):271-280 e278.
Preprint: Yamamoto, et al. bioRxiv.

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SHAKE, BOY, SHAKE!
ARE YOU INSANE?

Remdesivir

- Inhibits viral RNA synthesis
- Investigational and not currently approved for any indication
- Preliminary data from NIAID and manufacturer-sponsored trials suggests potential benefit
- Randomized, double-blind, placebo-controlled trial (Wang, *et al.*) found no statistically significant clinical benefits

Grein, et al. NEJM. 2020. Goldman, et al. NEJM, 2020. Wang, et al. Lancet. 2020.

Preliminary Results of ACCT-1

- Double-blind, randomized, placebo-controlled trial in hospitalized patients with evidence of LRTI
- Remdesivir group had shorter time to recovery (median 11 vs. 15d)
- Mortality lower in remdesivir group but not statistically significant -> reported at day 14 currently

Beigel, et al. *N Engl J Med.* 2020.

Topline Results of 2nd SIMPLE Trial

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Remdesivir

- NIH guidelines recommend for hospitalized patients with severe disease
  - SpO2 ≤94% on room air
  - Requiring supplemental O2, mechanical ventilation or ECMO

- NOT recommended for mild or moderate disease outside of a clinical trial

Obtaining remdesivir

- FDA Emergency Use Authorization

Remdesivir Allocation

- Oregon's Federal Redesivir Allocation: Patient Criteria and Hospital Distribution
- Hospital Agreement Form
- Last Mile Delivery User Guide for Shipping Remdesivir from OHA to Hospitals
- Fact Sheet for Health Care Providers: EUA of Remdesivir
- For patients:
  - Remdesivir Use for COVID-19 in Oregon – FAQ available in multiple languages
  - Fact Sheet for Patients and Parent/Caregivers – EUA of Remdesivir For Coronavirus Disease
    - Spanish Fact Sheet

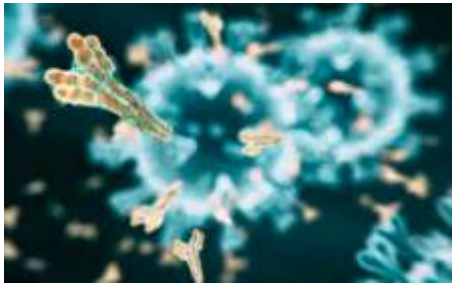
Remdesivir EUA Criteria

- Suspected or confirmed SARS-CoV-2 infection by PCR
- Hospitalized
- Severe COVID-19 disease defined by ≥1 of following
  - SpO2 ≤94% on room air
  - Requiring supplemental oxygen
  - Requiring mechanical ventilation or ECMO
- Exclusion criteria include GFR <30, renal replacement therapy, ALT or AST ≥5x ULN

Remdesivir Compassionate Use

- https://rdvcu.gilead.com/
- Not accepting new individual compassionate use requests
- Exceptions for pregnant pts and children <18yo with confirmed COVID-19 and severe disease

Convalescent Plasma



- Effect mediated via variety of mechanisms
- Early, limited data suggest a possible benefit
- Risks associated with the administration of plasma
- Multiple clinical trials ongoing

Shen, et al. *JAMA.* 2020.
Duan, et al. medRxiv. 2020.

Guidelines - Convalescent Plasma

- NIH: Insufficient data to recommend for or against the use of convalescent plasma for treatment of COVID-19

- IDSA: recommended in context of a clinical trial for hospitalized patients

Convalescent Plasma

- Pathways available for use:
  - Clinical trials
  - Expanded access program
  - Individual patient emergency IND

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

Convalescent Plasma EAP

- https://www.uscovidplasma.org/physicians-steps

- Inclusion criteria
  - ≥18yo (if <18yo, contact FDA for EIND)
  - Laboratory confirmed dx of COVID-19
  - Hospitalized
  - Severe or life-threatening COVID-19 or at high risk of progression to severe or life-threatening disease
  - Informed consent (form available at www.uscovidplasma.org)

Adjunctive therapies

- Immunomodulatory agents
  - Corticosteroids
  - IL-1 inhibitors (anakinra)
  - IL-6 inhibitors (sarilumab, siltuximab, tocilizumab)
  - Interferons
  - Janus kinase (JAK) inhibitors (baricitinib)

Corticosteroids

- **NOT** recommended with exception of ARDS due to COVID-19 in the context of a clinical trial
- Retrospective studies in COVID pneumonia show variable benefit but study limitations don't allow determination of tx effect
- Previous data from SARS suggest potential harm (delayed viral clearance)

Immunomodulatory Agents

- Insufficient data to recommend for or against IL-1 or IL-6 inhibitors

- Clinical trials ongoing

Antibiotics

- **Mild**: NOT recommended
- **Moderate**: NOT recommended unless bacterial infection suspected

- **Severe**:
  - Surviving sepsis: suggested in pts requiring mechanical ventilation for respiratory failure (weak rec, low quality evidence)
  - NIH: insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication (BIII)

- **If started, re-assess daily for de-escalation**

Concomitant Medications

- Continue ACE inhibitors, ARBs, statins for pts already on these medications
- Pts taking NSAIDs for co-morbid condition should continue as previously directed by their provider

Resources

- IDSA Treatment Guidelines: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
- NIH Treatment Guidelines: https://covid19treatmentguidelines.nih.gov/introduction/
- WHO Guidelines: https://www.who.int/publications-detail/clinical-management-of-covid-19
- OHA: https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/DISEASESAZ/Pages/COVID-19.aspx
- Society of Critical Care Medicine: https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19
- Clinical Trials: https://clinicaltrials.gov/

Thanks!