PRISMA HEALTH SM

Observations Regarding COVID 19

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"Can you give a talk on what we have learned from or during COVID-19?"

"So, how are we going to carve this turkey?"

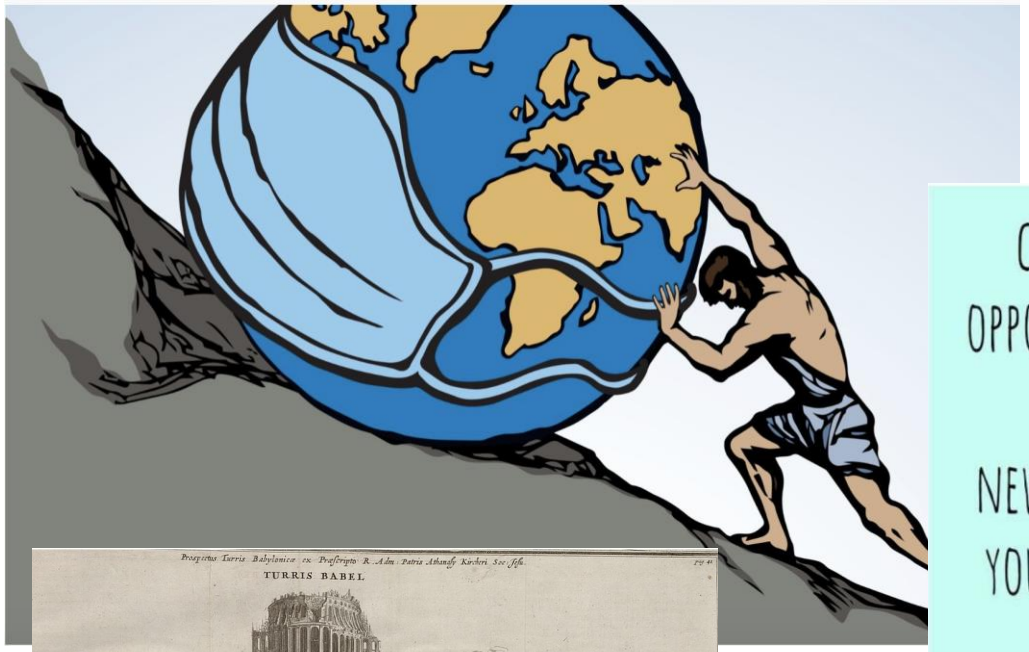
Goals of this talk

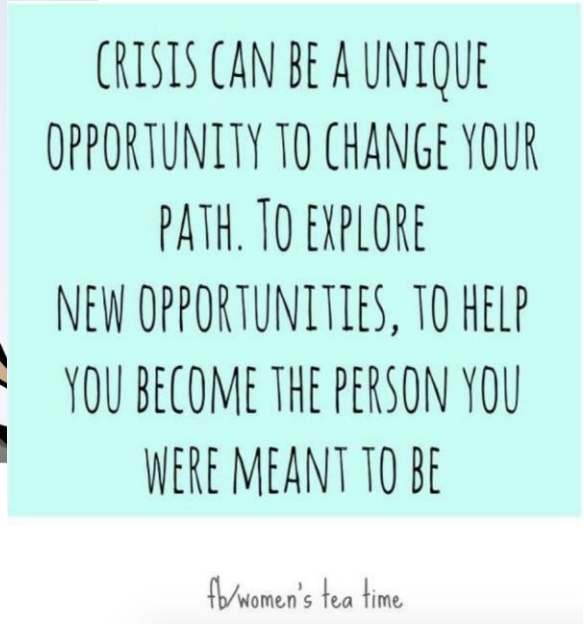
- Between the two of us we wanted to cover:

1. **Vaccine data** (Bill)
2. **Controversial therapies** (Mark)
3. **Post-Covid syndrome, aka "long-covid"** (Mark)
4. **What the future holds? Variants on the horizon** (Bill)
5. **Leave plenty of time for questions**

Disclosures

- None financial





Controversial Therapies

- This pandemic has not favored a methodical and scientific process.
- Desperate times, desperate measures?
- Treatments come and treatments go
- The impact of social media and politics?
- How has Pharma impacted this?

Ivermectin

- Inhibits viral replication in vitro
- As with many other highly-protein bound drugs, ivermectin has an effective concentration for killing SARS-COV2 (EC50) that cannot be achieved in humans using safe doses
- Patient harm has occurred after using livestock preparations
- Can interfere with warfarin
- Prescriptions of ivermectin have increased twenty-four-fold in the United States from March 2019 to August 2021

> Cochrane Database Syst Rev. 2021 Jul 28;7(7):CD015017.
doi: 10.1002/14651858.CD015017.pub2.

Ivermectin for preventing and treating COVID-19

Maria Popp [1], Miriam Stegemann [2], Maria-Inti Metzendorf [3], Susan Gould [4], Peter Kranke [1], Patrick Meybohm [1], Nicole Skoetz [5], Stephanie Weibel [1]

Affiliations + expand

PMID: 34318930 PMCID: PMC8406455 DOI: 10.1002/14651858.CD015017.pub2
Free PMC article

- 14 studies with 1678 participants; **compared to no treatment, placebo, or standard of care.**
- **No study** compared ivermectin to an intervention with proven efficacy.
- **9** studies, moderate COVID-19 in **inpatient** settings
- **4** studies, mild COVID-19 cases in **outpatient** settings.
- **1** study investigated **prevention**
- **8** studies, **open-label** design
- **6** studies, **double-blind and placebo-controlled.**

- Of the 41 study results contributed by included studies, about **one third were at overall high risk of bias.**
- *We are uncertain whether ivermectin compared to placebo or standard of care reduces or increases mortality, clinical worsening up to day 28, adverse events within 28 days, and viral clearance at day seven*

Cochrane Review Continued:

- For outpatient COVID-19 treatment?
  - *We* are **uncertain** whether ivermectin compared to placebo or standard of care reduces or increases...
- For prevention?
  - We found one study.
  - Mortality up to 28 days was the only outcome eligible for primary analysis.
  - *We are **uncertain** whether ivermectin reduces or increases mortality compared to no treatment*

Cochrane Review Continued:

- Reviewed pooled data from **16 randomized controlled trials** (total enrolled 2407), including both inpatients and outpatients.
  - Evidence on whether ivermectin reduces mortality, need for mechanical ventilation, need for hospital admission and time to clinical improvement in COVID-19 patients is of *"very low certainty,"*
    - due to the small sizes and methodological limitations of available trial data, including small number of events.

- **Did not look at the use of ivermectin to prevent** COVID-19, which is outside of scope of the current guidelines.

> Cochrane Database Syst Rev. 2021 Aug 5;8(8):CD014962. doi: 10.1002/14651858.CD014962.

Remdesivir for the treatment of COVID-19

Kelly Ansems [1], Felicitas Grundeis [2], Karolina Dahms [1], Agata Mikolajewska [3], Volker Thieme [4], Vanessa Piechotta [5], Maria-Inti Metzendorf [6], Miriam Stegemann [3], Carina Benstoem [1], Falk Fichtner [4]

Affiliations + expand

PMID: 34350582 PMCID: PMC8406992 (available on 2022-08-05)
DOI: 10.1002/14651858.CD014962

- **Moderately certain,** has **little or no effect** on all-cause mortality at up to day 28 in hospitalized adults.

- **Uncertain** on clinical improvement and worsening. Insufficient data available to validly examine the effect of remdesivir on mortality in subgroups depending on the extent of respiratory support at baseline.

  - Considering the initial severity of condition, only one study showed a beneficial effect of remdesivir in patients **who received low-flow oxygen at baseline** (RR 0.32, 95% CI 0.15 to 0.66, 435 participants), but conflicting results exists from another study, and we were unable to validly assess this observations due to limited availability of comparable data.

- **May decrease** the risk of clinical worsening in terms of new need for invasive mechanical ventilation

- **Probably decreases** the serious adverse events rate at up to 28 days

Meta-Analysis > Cochrane Database Syst Rev. 2021 Feb 12;2(2):CD013587.
doi: 10.1002/14651858.CD013587.pub2.

Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19

Bhagteshwar Singh [1 2 3], Hannah Ryan [4], Tamara Kredo [5], Marty Chaplin [6], Tom Fletcher [6]

Affiliations + expand

PMID: 33624299 PMCID: PMC8094389 DOI: 10.1002/14651858.CD013587.pub2
Free PMC article

- **Infected**: little or no effect on the risk of death and probably no effect on progression to mechanical ventilation. **Adverse events are tripled** compared to placebo, but very few serious adverse events were found.

- **Preventing** - Ongoing trials are yet to report results for this objective
  - We are very uncertain about the effect of HCQ on the primary outcomes, for which few events were reported: 20/821 (2.4%) developed confirmed COVID-19 at 14 days from enrolment, and 2/821 (0.2%) were hospitalized due to COVID-19 (**very low-certainty evidence**).

HCQ and CQ continued:

- **Non-hospitalized** patients with asymptomatic or mild COVID-19, **has not been shown** to reduce SARS-CoV-2 RNA viral load or disease progression in several small randomized trials (Skipper, October 2020; Mitja, July 2020).
- **PEP**: RCT/PCT of 821 participants in the US, **no impact** (within four days of a high-risk exposure) (Boulware, August 2020).
- Several RCTs: **hospitalized** patients, **have not shown clinical benefit,** nor have RCTs focused on PEP

Review > Cochrane Database Syst Rev. 2021 Aug 16;8(8):CD014963.
doi: 10.1002/14651858.CD014963.

Systemic corticosteroids for the treatment of COVID-19

Carina Wagner [1], Mirko Griesel [2], Agata Mikolajewska [3], Anika Mueller [4], Monika Nothacker [5], Karoline Kley [2], Maria-Inti Metzendorf [6], Anna-Lena Fischer [7], Marco Kopp [1], Miriam Stegemann [3], Nicole Skoetz [8], Falk Fichtner [2]

Affiliations + expand

PMID: 34396514 PMCID: PMC8406706 (available on 2022-08-16)
DOI: 10.1002/14651858.CD014963

- **Moderate-certainty**: slightly reduce **all-cause mortality** in hopsitalized
- **Low-certainty**: May also be a reduction in **ventilator-free days**.
- **No evidence**: Asymptomatic or mild disease (**non-hospitalized** participants).

WHO's Assessement

- **Strong recommendation for** the use systemic **corticosteroids** for severe or critically ill COVID-19 patients; with a c**onditional recommendation against** their use in patients with mild/moderate COVID-19

- **Conditional recommendation against** administering **remdesivir** in addition to usual care.

- **Strong recommendation against** the use of **hydroxychloroquine or chloroquine** for treatment of COVID-19 of any severity

- **Strong recommendation against** administering **lopinavir/ritonavir** for treatment of COVID-19 of any severity

- **Conditional recommendation for** the use of **low dose anticoagulants** in hospitalized patients

Fluvoxamine

- Stimulates **sigma-1 receptors** on the surface of the **endoplasmic reticulum**, which processes and traffics proteins within cells.
- Results in **dampened inflammatory response** to sepsis in laboratory animals, and has also been shown to **block SARS-CoV-2 replication** (Hashimoto, March 2021)
- **Inhibition of platelet activation** and its targeting of lysosomes (Homolak, August 2020; Schlienger, May 2003)
- A much larger recent RCT in Brazil, called the TOGETHER trial, was released as a preprint in late August 2021.
  - **Symptomatic** adults: fluvoxamine (100 mg PO BID x 10 days) or placebo;
    - the **primary endpoint** was extended observation in the ED or hospitalization
      - 739 participants received fluvoxamine and 733 received placebo.
      - Observed lower rate of hospitalization in the fluvoxamine (10.4%) than in the placebo group (14.7%) (ITT RR 0.71; 95% Bayesian CI 0.54-0.93)

WHO Solidarity Plus Trial

- In late 2021, the WHO plans to launch a new phase of its Solidarity PLUS trial in 52 countries to test 3 drugs:
  - ***Artesunate*** (an FDA-approved antimalarial used in intravenous form for the treatment of severe malaria),
  - ***Infliximab*** (an FDA-approved monoclonal antibody which blocks TNF alpha)
  - ***Imatinib*** (an FDA-approved signal transduction inhibitor/tyrosine kinase inhibitor used for the treatment of Philadelphia chromosome positive leukemias).

Artesunate

- May have both antiviral and immunomodulatory effects
- Theorized to be due to its **inhibition of endocytosis of virus**, NF-kappa B mediated **dampening of cytokines** such as TNF-alpha, IL-6, and IL-1, and its **inhibition of MMP-2 and MMP-9** (Magenta, December 2014; Xu, February 2007).
- In vitro activity with clinically achievable EC50 values (Cao, July 2020).
- 43 patients reported statistically improved clinical outcomes in the artesunate group as compared to the control group (Lin, April 2020).

Infliximab

- Patients receiving various types of immune inhibitors have attenuated cases of COVID-19.

- The SECURE-BID registry found that patients with IBD on anti-TNF antibodies had **lower risk of death or hospital admission** than those not on these agents (aOR 0.60 [95% CI 0.38-0.96], p=0.03) (Brenner, August 2020).

- The COVID-19 Global Rheumatology Alliance registry likewise found that patients on anti-TNF agents +/- other immunomodulators had **lower rates of hospital admissions** (aOR 0.40 [95% CI 0.19-0.80], p=0.01) (Gianfrancesco, July 2020).

Imatinib

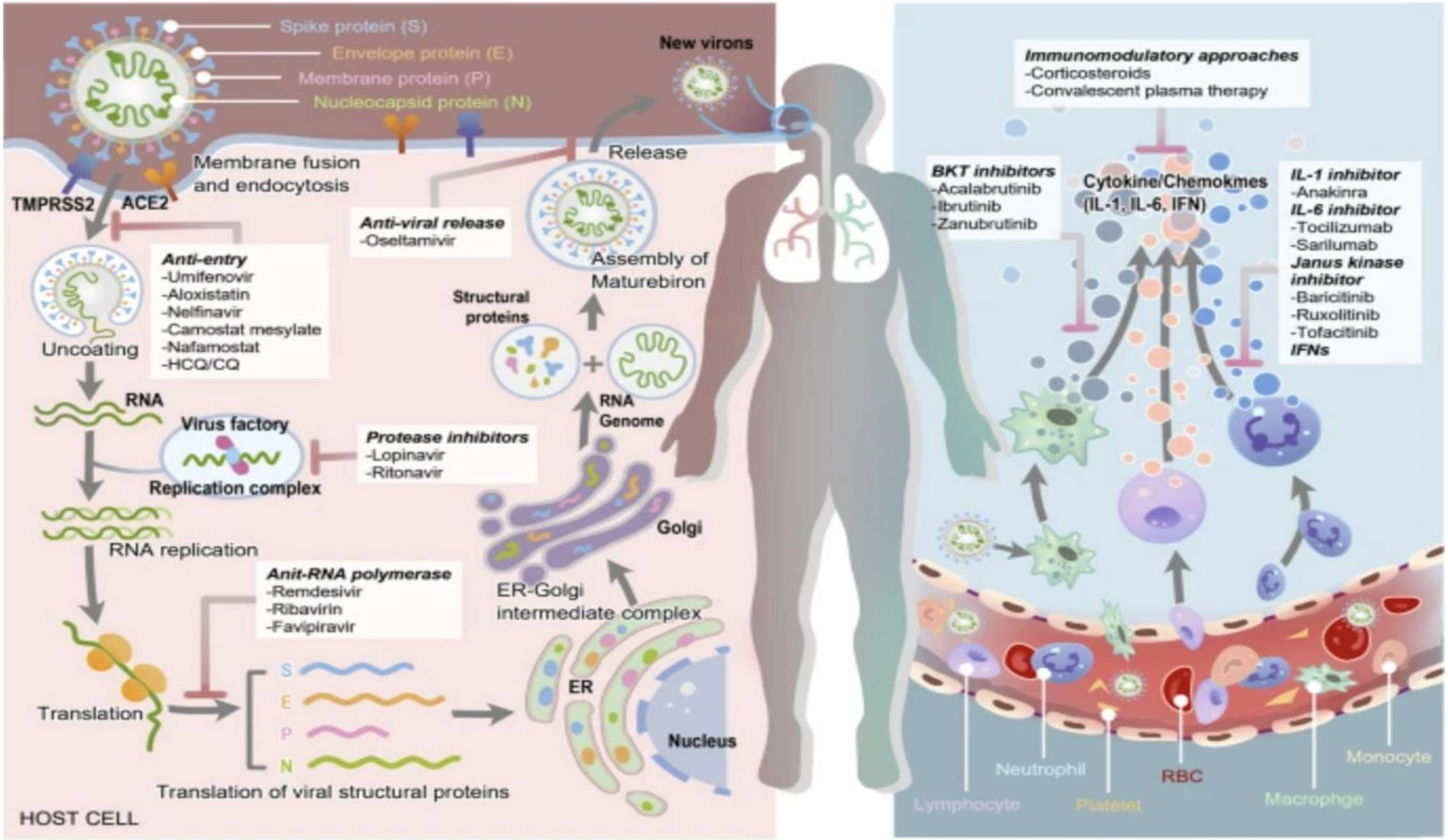
- Mechanistic studies have noted that the SARS-CoV and possibly SARS-CoV-2 viruses rely on **ABL2 kinases** to infect host cells, and therefore that **blocking this kinase specifically might have antiviral activity** (Sisk, May 2018; Coleman, September 2016).

- Early clinical data suggested that imatinib **may stop pulmonary capillary leak** and confer clinical benefit to patients **hospitalized** with COVID-19 (Aman, June 2021).

- RPCT of 385 participants hospitalized found a **lower 28-day mortality** in the imatinib group than in the placebo group (HR 0.51 [0.27-0.95]),
  - but when factors associated with mortality were controlled for, **aHR was non-significant** at 0.52 (95% CI 0.26-1.05).
  - Significantly **shorter duration of mechanical ventilation** requirement in the imatinib group than the placebo group (median duration 7 days [3–13] vs. 12 days [IQR 6–20] respectively; p=0·0080),
  - Also **shorter length of intensive care unit stay** in the imatinib group (median duration 8 days [5–13] vs. 15 days [7–21] in the placebo group; p=0·025).
  - Notably, 276 of the 385 study participants (**72%) also received dexamethasone**.

Other Drugs

- block the binding of **ACE2 and the receptor-binding domain** include *nobiletin, glycyrrhizin, neohesperidin and SSAA09E2*.
- **"naturally occurring" compounds** have been shown to inhibit SARS-CoV-2 **in vitro** (*resveratrol, ginkgolic acid, baicalein*) and also to **synergistically augment** antiviral effect when used in combination with existing antivirals (*linoleic acid + remdesivir; cepharanthine plus nelfinavir*) (Yang, June 2021).
- direct antivirals (other than remdesivir) include **nucleoside/nucleotide analogues**, such as *favipiravir* (an RdRp blocker that has approval in Japan for the treatment of influenza


Spike protein (S)
Envelope protein (E)
Membrane protein (P)
Nucleocapsid protein (N)
New virons
Release
Membrane fusion
and endocytosis
TMPRSS2
ACE2
Anti-viral release
-Oseltamivir
Assembly of
Maturebiron
Structural
proteins
RNA
Genome
Anti-entry
-Umifenovir
-Aloxistatin
-Nelfinavir
-Camostat mesylate
-Nafamostat
-HCQ/CQ
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Protease inhibitors
-Lopinavir
-Ritonavir
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intermediate complex
Anit-RNA polymerase
-Remdesivir
-Ribavirin
-Favipiravir
ER
Translation
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Nucleus
Translation of viral structural proteins
HOST CELL
Immunomodulatory approaches
-Corticosteroids
-Convalescent plasma therapy
BKT inhibitors
-Acalabrutinib
-Ibrutinib
-Zanubrutinib
Cytokine/Chemokines
(IL-1, IL-6, IFN)
IL-1 inhibitor
-Anakinra
IL-6 inhibitor
-Tocilizumab
-Sarilumab
Janus kinase
inhibitor
-Baricitinib
-Ruxolitinib
-Tofacitinib
IFNs
Neutrophil
RBC
Monocyte
Lymphocyte
Platelet
Macrophge

Therapeutics Under Early Investigation

Last updated: February 24, 2021

There are many therapeutics under early investigation for treatment of COVID-19 for which there is currently insufficient clinical data to recommend either for or against. This overview is not a comprehensive summary, but a list of therapeutics with strong biological plausibility that are available in the United States and are or will be studied by clinical trial.

Class/Drug	Mechanism of Action	Notable Publications*
Anakinra	• Interleukin (IL)-1 receptor antagonist; blocks activity of the proinflammatory cytokines IL-1α and IL-1β.	Cavalli, June 2020 Huet, May 2020
Baricitinib	• Janus kinase (JAK) 1 and 2 inhibitor; inhibits JAK1-2 mediated cytokine release. • Disrupts endocytosis regulators and cyclin G-associated kinase; may reduce inflammation and interfere with intracellular virus assembly.	Cantini, April 2020
Colchicine	• Exhibits broad anti-inflammatory and immunomodulatory properties. • Disrupts microtubule formation and reduces chemotaxis, phagocytosis and migration of neutrophils.	Tardif, January 2021 Della-Torre, August 2020 Lopes, August 2020 Gendelman, July 2020 Deftereos, June 2020
Interferons	• Modulate the immune response in specific—not all—viral infections. • Bind to interferon-α and -β receptors on the cell membrane, resulting in various transcription factor phosphorylation. Subsequent activation of interferon-stimulated genes leads to immunomodulatory effects and interference with viral replication.	Monk, November 2020 Wang, July 2020 Davoudi-Monfared, May 2020 Zhou, May 2020 Hung, May 2020
Intravenous immunoglobulin	• Derived from pooled plasma; contains antibodies typically present in adult human blood. • May provide passive immune protection from viral infections via modulation of inflammation.	Sakoulas, November 2020 Gharebaghi, October 2020 Xie, August 2020 Sakoulas, July 2020 Shao, April 2020
Ruxolitinib	• Janus kinase (JAK) 1 and 2 inhibitor; inhibits JAK1-2 mediated cytokine release. • Disrupts endocytosis regulators and cyclin G-associated kinase; may reduce inflammation and interfere with intracellular virus assembly.	
Statins	• Statins have anti-inflammatory and immunomodulatory properties that may allow for lung protection in the setting of infection.	Zhang, August 2020 Kow, August 2020 De Spiegeleer, July 2020
Calcifediol/Vitamin D	• Prohormone of the active form of vitamin D3, calcitriol (1,25-dihydroxyvitamin D3).	Murai, February 2021 Patchen, February 2021 Castillo, October 2020

Post-COVID Syndrome (ie. Long-Covid)

- Symptoms develop during or after acute COVID-19 illness, continue for **≥4 weeks**, and are not explained by an alternative diagnosis
  - fatigue, dyspnea, chest pain, and cough. Headache, joint pain, insomnia, anxiety, cognitive dysfunction, myalgias, and diarrhea

- **10% of patients** develop long COVID (*JAMA*, Vol. 225, No. 19, 2021; The *BMJ*, Vol. 370, No. 8258, 2020

- Further divided into two periods:
  - (1) clinical and laboratory abnormalities that **persist 4–12 weeks** beyond acute COVID-19; and (2) clinical and laboratory abnormalities persisting **>12 weeks beyond** acute COVID-19 and not attributable to alternative diagnoses (Shah, January 2021).

- In one recent study in Wuhan, China, **6 months after** acute infection and hospitalization:
  - **63%** reported **fatigue or muscle weakness**,
    - **26%** reported **sleep difficulties**
    - **23%** reported **anxiety or depression** (*The Lancet*, Vol. 397, No. 10270, 2021)

- A May 2021 study found in the 6 months post infection: **33%** had n**eurological or psychological symptoms** (*The Lancet Psychiatry*, Vol. 8, No. 5, 2021

Post-Covid Syndrome (PCS) Continued

- **Prevention is optimal**, and data is starting to note that vaccination reduces the risk
- Risk increases with **older age**, greater number of **co-morbidities,** and those with **severe illness** requiring ICU care.
- February, the National Institutes of Health announced a 4-year, $**1.15 billion** initiative to study
- ***"If we only focus on recovery from the virus, and not recovery from a holistic, whole-person perspective, people's recovery is going to be incomplete,"***
    - Megan Hosey, PhD, an assistant professor of rehabilitation psychology and neuropsychology in the Johns Hopkins Department of Physical Medicine and Rehabilitation.

PCS Continued

- **Heart.** Imaging tests taken months after recovery from COVID-19 have shown **lasting damage to the heart muscle**, even in people who experienced only mild COVID-19 symptoms. This may increase the risk of heart failure or other heart complications in the future.

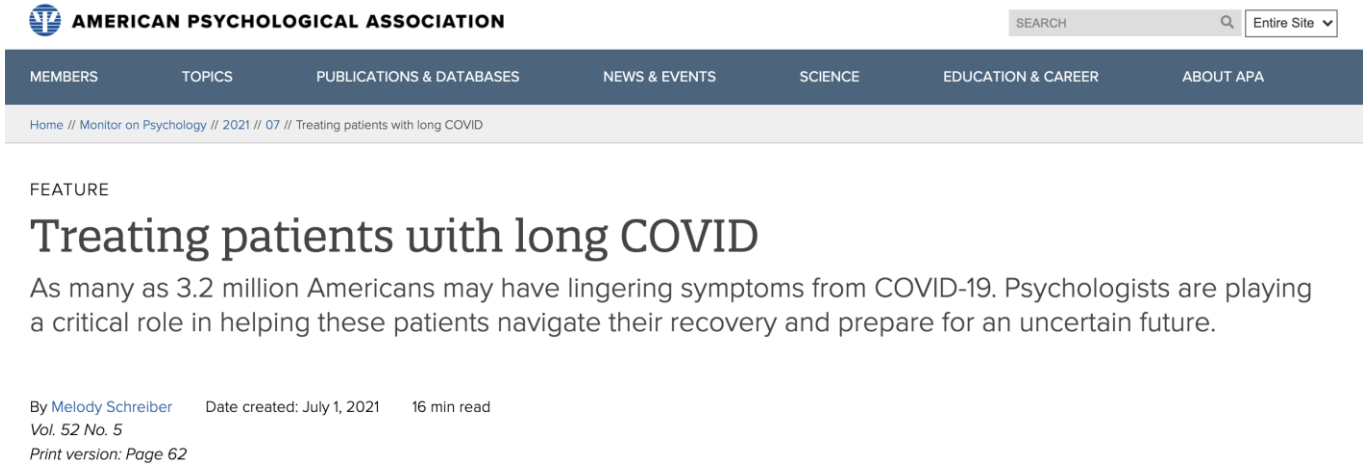
- **Lungs.** The type of pneumonia often associated with COVID-19 can cause **long-standing damage to alveoli**. The resulting scar tissue can lead to long-term breathing problems.

- **Brain.** Even in young people, COVID-19 can cause **strokes, seizures and Guillain-Barre syndrome.** COVID-19 may also increase the risk of developing **Parkinson's disease** and **Alzheimer's disease**.

Guidance on “Long COVID” as a Disability Under the ADA, Section 504, and Section 1557

U.S. Department of Health Human Services
Office for Civil Rights

U.S. Department of Justice
Civil Rights Division
Disability Rights Section



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Home // Monitor on Psychology // 2021 // 07 // Treating patients with long COVID

FEATURE

Treating patients with long COVID

As many as 3.2 million Americans may have lingering symptoms from COVID-19. Psychologists are playing a critical role in helping these patients navigate their recovery and prepare for an uncertain future.

By Melody Schreiber Date created: July 1, 2021 16 min read
Vol. 52 No. 5
Print version: Page 62

- Similarities with other chronic illnesses, such as chronic fatigue syndrome, dysautonomia, etc...
- **Denial** in the medical system has resulted in many people avoiding care.
  - **“They would rather suffer in silence than risk what they perceive to be the scorn and rejection of the medical establishment,”**
    - James C. Jackson, PsyD, director of behavioral health at Vanderbilt University Medical Center’s ICU Recovery Center.

PCS Continued

- Start by asking about their most prominent concerns. Which parts of their illness most affect their lives?
  "What are you hoping to get back to?" and *"If you weren't sick, what would you do today?"*

- **Mood can alter pain perception**. Think of stubbing your toe on the best day of your life versus the worst day—the experience can feel much different.

- CBT, peer/support groups, mindfullness, neuropsych intervention, family therapy, acceptance and commitment therapy

- *"As a society, we spend freely on saving lives in the emergency room and the ICU, but the money dries up when the patients need it most, after they've survived,"*

- *"If there is a moral imperative to save lives, there is also a moral imperative to provide the treatments that make those lives full again."*

PCS Continued

- https://www.nice.org.uk/guidance/ng188

- Screening questionaire?
  - Yorkshire rehab questionnaire
  - Newcastle screening tool (see appendix B)

- *Use a holistic, person-centred approach. Include a comprehensive clinical history and appropriate examination that involves assessing* ***physical, cognitive, psychological and psychiatric symptoms, as well as functional abilities****.*

- Be aware that people can have wide-ranging and fluctuating symptoms after acute COVID-19, which can change in nature over time.

Questions?


Strategy Starts with Asking the Right Questions
WHAT
WHERE
WHEN
WHY

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Thank you for your time