COVID-19 Literature Update

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UW Global and Rural Health Fellow

11/13/2020

Disclosure

- I am not an infectious disease specialist
- COVID-19 research is dynamic, and this may soon be out of date
- However, I am a recent internal medicine / pediatrics trained physician with experience caring for patients with COVID-19 infection ranging from the outpatient to ICU settings

Objectives

- Review major published work focused on COVID-19, with focus on:
  - Treatment
  - Vaccine development
  - Coagulopathy
  - Waning immunity and reinfection

Treatment

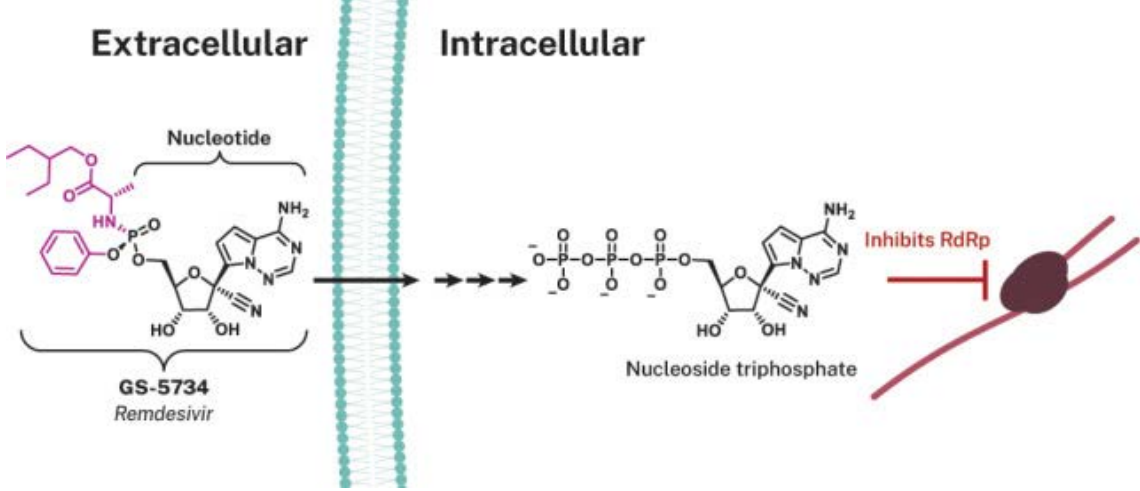
Big Picture

- A lot of initial treatment was initially off label, but now increasingly RCTs are guiding therapy
- No game changing therapies yet
  - Mostly hope for improving / shortening symptoms
- Existing therapies have not yet been shown to decrease transmission
- There is greater impact on improving access to care and ICUs than accessing treatments at this time

Two superimposed diseases

- Viral infection
  - Early in course
  - Due to host response to virus
  - As viral shedding decreases, symptoms improve
  - Antiviral therapies indicated (e.g. remdesivir, monoclonal antibodies)
- Immune response
  - Later in course
  - Due to ongoing inflammation after viral replication declines
  - Exuberant host response likely contributes to most severe cases
  - Anti-inflammatory therapies indicated (e.g. dexamethasone)

Antiviral - remdesivir

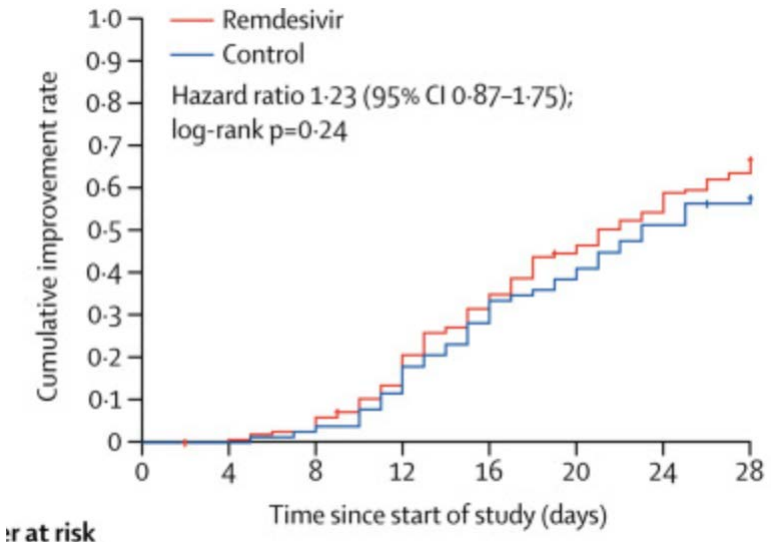


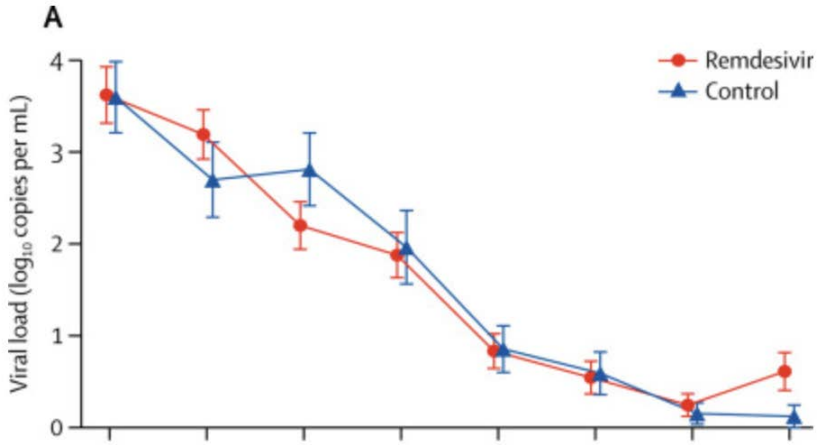
- Nucleotide analog that blocks RNA polymerase, preventing virus from replicating its genome
- Effective against RNA viruses (SARS, ebola, etc.)
- Developed in early 2010s
- Given recent established clinical trials with efficacy against ebola and MERS, was adopted early to treat COVID-19 under compassionate use

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

May 16, 2020

- 237 patients with severe infection at 10 hospitals in Hubei, China
  - Did not reach target recruitment due to decrease in case numbers
- Trend towards faster recovery time with remdesivir





Wang Y et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020 May 16;395(10236):1569-1578

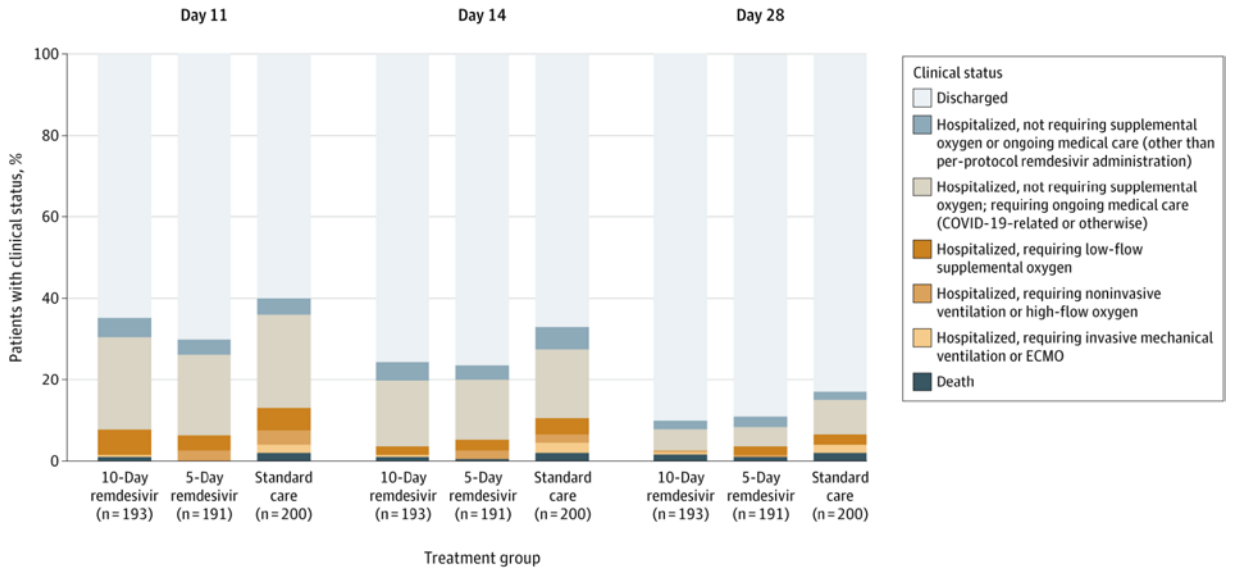
JAMA | Original Investigation

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19

A Randomized Clinical Trial

August 21, 2020

- 584 patients hospitalized with moderate infection across 105 sites
  - US, Europe, Asia
- Randomized 1:1:1 to 10 day course, 5 day course, and placebo
- 5 day course had significantly higher odds of better clinical status on day 11

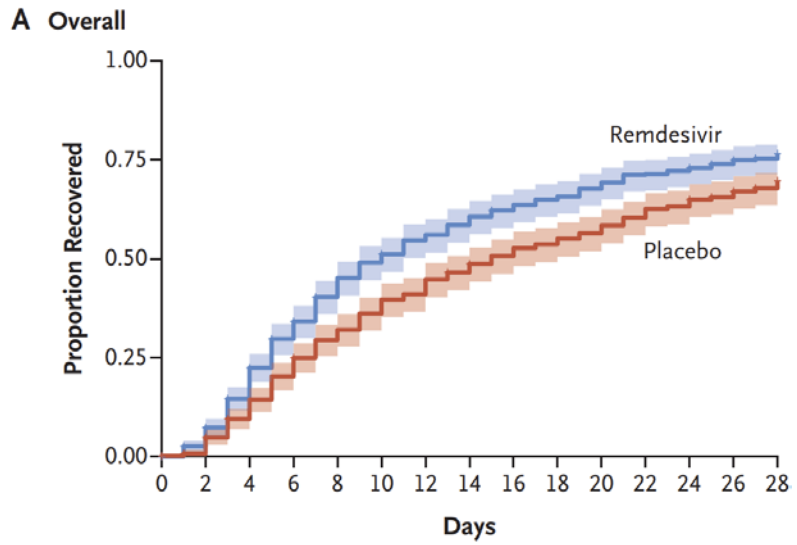


Spinner CD et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19. JAMA. 2020;324(11):1048-1057.

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Final Report

NOVEMBER 5, 2020



- Adaptive Covid-19 Treatment Trial (ACTT-1)
- 1062 hospitalized patients across 60 sites
  - US, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore
- Remdesivir shortened median time to recovery (10 days vs 15 days)
- Trend towards decreased mortality (11.4% vs 15.2%) at day 29
- Less benefit in intubated / ECMO patients, consistent with mechanism

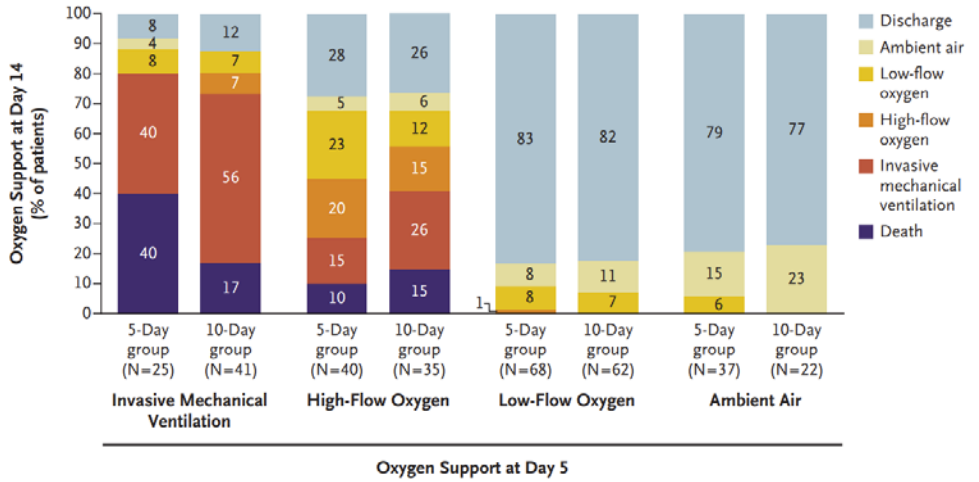
Beigel JH et al. Remdesivir for the Treatment of Covid-19 — Final Report. N Engl J Med. 2020 Oct 8: NEJMoa2007764.

ORIGINAL ARTICLE

Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

NOVEMBER 5, 2020

- 397 hospitalized patients with severe infection across 55 sites
  - US, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, Taiwan
  - No mechanical ventilation / ECMO patients at enrollment
- At baseline, 10 day group had significantly worse clinical status
- There was no significant difference between a 5 and 10 day treatment course



Goldman JD et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med. 2020 Nov 5: NEJMoa2015301.

FDA NEWS RELEASE

FDA Approves First Treatment for COVID-19

October 22, 2020

- FDA approved remdesivir for hospitalized patients >12 years old and >40kg
- EUA still active for hospitalized pediatric patients 3.5-40kg

Antiviral – convalescent plasma

- Passive immunization from plasma of survivors
- Demonstrated efficacy in other conditions (rabies, hep B)
- Nonspecific with numerous antibodies against many epitopes
- Many cons
  - Hard to collect in large quantities
  - Antibodies may decrease from time of testing to time of apheresis
  - Variability in content of plasma
  - Safety issues
- Due to EUA, limited enrollment in clinical trials

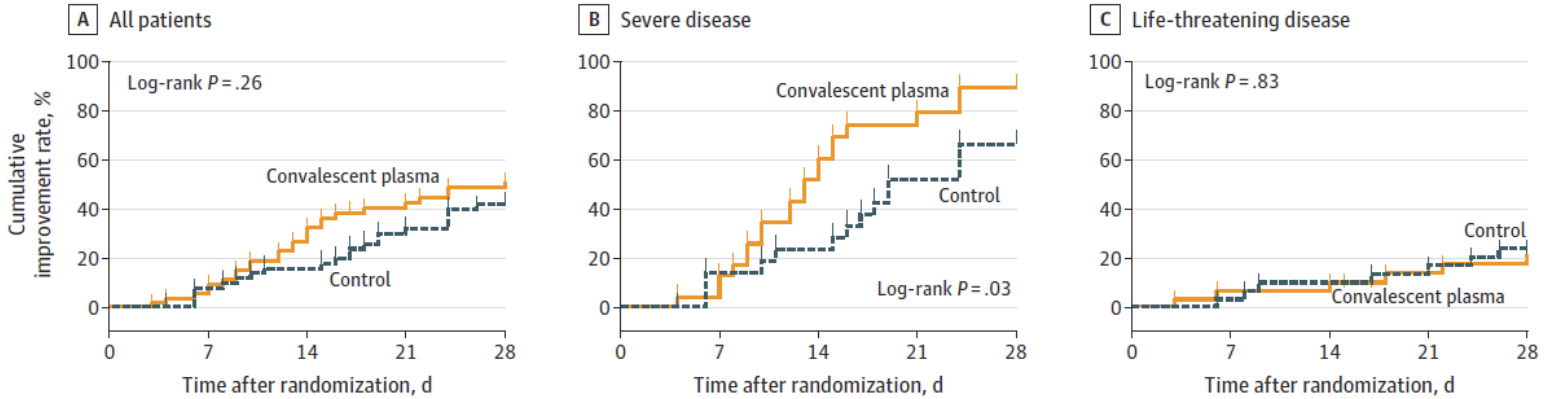
JAMA | Original Investigation

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19

A Randomized Clinical Trial

June 3, 2020

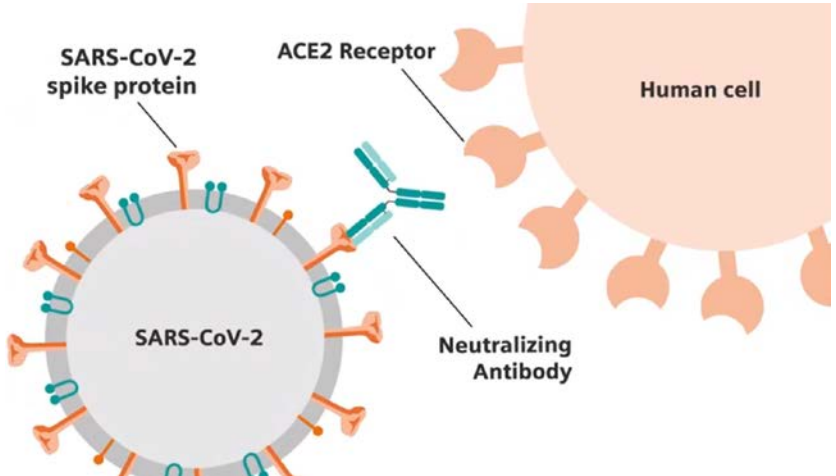
- 103 patients with severe infection at 7 hospitals in Wuhan, China
  - Did not reach target recruitment due to decrease in case numbers
- Significant decreased time to clinical improvement in those with severe disease
- Increased negative conversion of PCR at day 3 (87% vs 37.5%)
- Less benefit in life-threatening cases, consistent with mechanism



Li L et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19. JAMA. 2020;324(5):460-470.

Antiviral – monoclonal antibody

- Pharmaceutically made, targeted monoclonal antibody
- More consistent, specific, and scalable than plasma
- May help understand what aspects of immunity are helpful
  - Current antibodies target the spike protein
  - Neutralizes virus in vitro and prevents infection of tissue cells
- However, does not replicate normal immune response

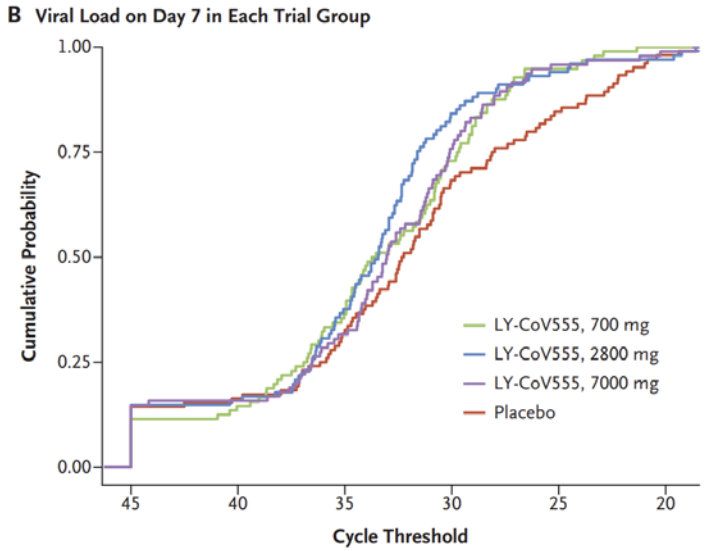


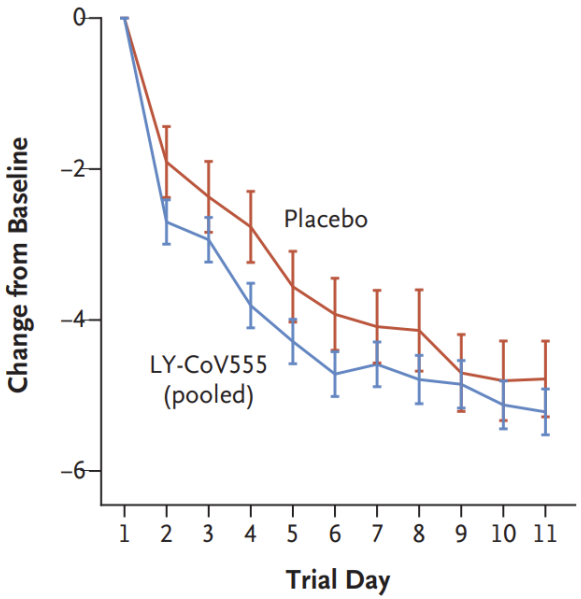
ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

October 28, 2020

- Phase II trial of 452 patients with mild-moderate infection
  - Randomized to low, medium, and high dose antibody or placebo
- Medium dose was associated with significant decreased viral load
- Patients who received the antibody reported lower severity symptoms on days 2-6
- 1.6% of patients who received antibody presented to the ED, compared to 6.3% in the placebo group





Chen P et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med. 2020 Oct 28. doi: 10.1056/NEJMoa2029849.

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibody for Treatment of COVID-19

November 09, 2020

- FDA issued EUA for bamlanivimab (Ly-CoV555) for the investigational treatment of mild-moderate COVID-19 infection in adults and kids
- Phase III trials to come

REGENERON

Regeneron's REGN-COV2 Antibody Cocktail Reduced Viral Levels and Improved Symptoms in Non-Hospitalized COVID-19 Patients

September 29, 2020

- REGN-COV2 is a combination of two monoclonal antibodies against two different epitopes on the spike protein
- No official peer reviewed published data yet
- Press release reports data from a Phase I / II / III trial in mild-moderate infection
- Significant reduction in viral load with high dose antibodies
- Effect greater in those who were seronegative and had higher viral loads at baseline
- Not yet available to the public

Anti-inflammatory - dexamethasone

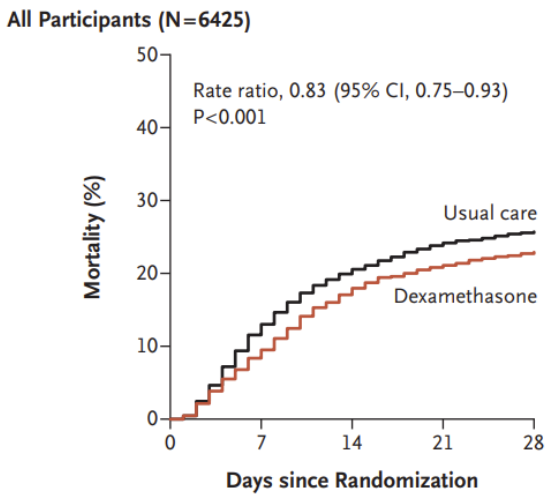
- “Blunt hammer” immunosuppression
- Globally available
- Cheap
- Well tolerated

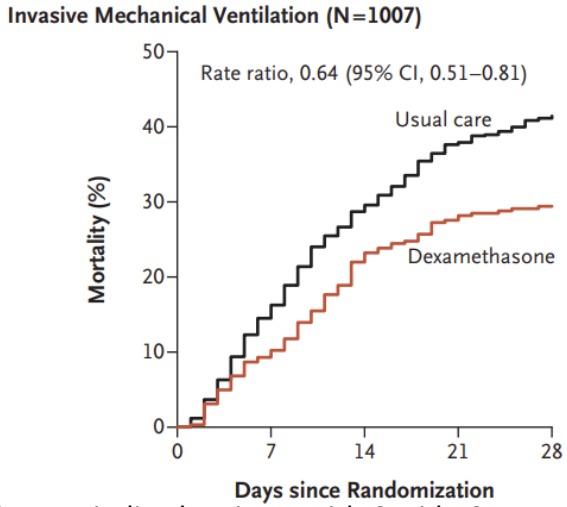
ORIGINAL ARTICLE

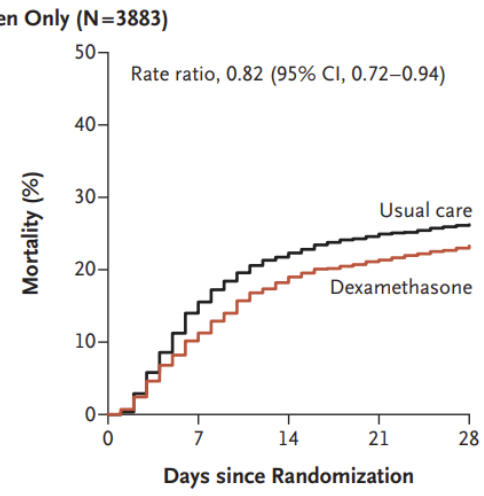
Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

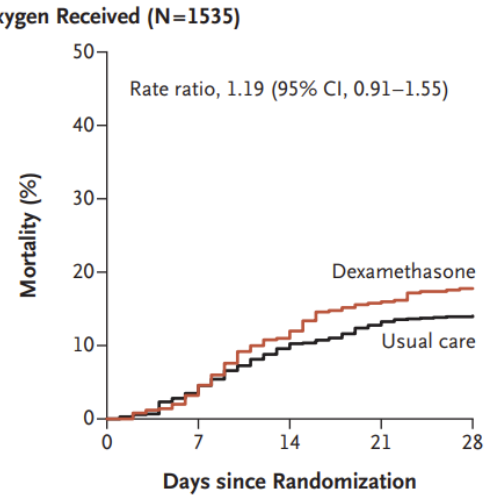
July 17, 2020

- RECOVERY trial
- 6425 hospitalized patients in the UK
- Randomized 1:2 to dexamethasone versus placebo
- Significantly lower mortality at 28 days
  - More benefit with increasing illness, no benefit if not requiring oxygen









RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. N Engl J Med. 2020 Jul 17;NEJMoa2021436 .

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19

A Meta-analysis

September 2, 2020

- Meta-analysis of 7 RCTs including 1703 critically ill patients from 12 countries
- Systemic corticosteroids were associated with lower mortality at 28 days
  - 32.7% versus 41.4%

REACT Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19. JAMA. 2020;324(13):1330-1341.

Anti-inflammatory - tocilizumab

- Monoclonal antibody against IL-6
- Interrupts inflammatory cascade
- Currently used for severe rheumatoid arthritis, JIA, and CAR T-cell cytokine release syndrome
- IL-6 has been shown to be markedly elevated

Effective treatment of severe COVID-19 patients with tocilizumab

May 19, 2020

- Retrospective analysis of 21 patients with severe to critical infection in one hospital in China that received tocilizumab
- Reportedly dramatic improvement in fever and clinical status
- 75% of patients had decreasing oxygen requirement on day 5
- 91% of patients had improving CT scans
- All patients survived to discharge

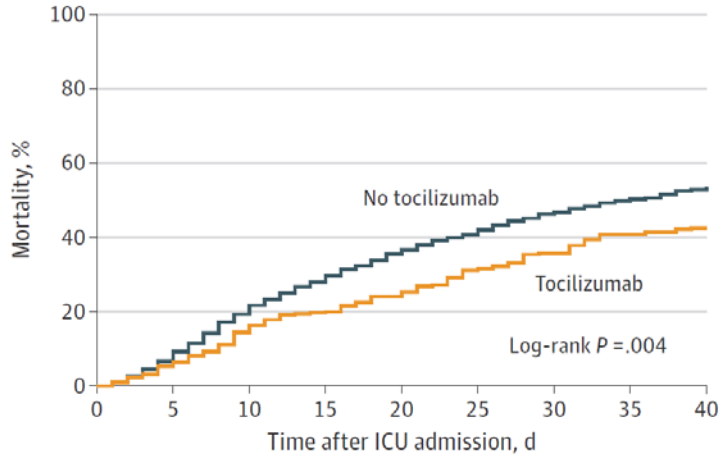
Xu X et al. Effective treatment of severe COVID-19 patients with tocilizumab. PNAS May 19, 2020 117 (20) 10970-10975.

JAMA Internal Medicine | Original Investigation

Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19

October 20, 2020

- Multicenter retrospective cohort study of 3924 critically ill patients across 68 hospitals in the US
- Patients were grouped into two groups
  - Those who received tocilizumab in the first two days of admission
  - Those who did not receive early tocilizumab
- Mortality rate was lower in the early tocilizumab group (29% vs 41%)



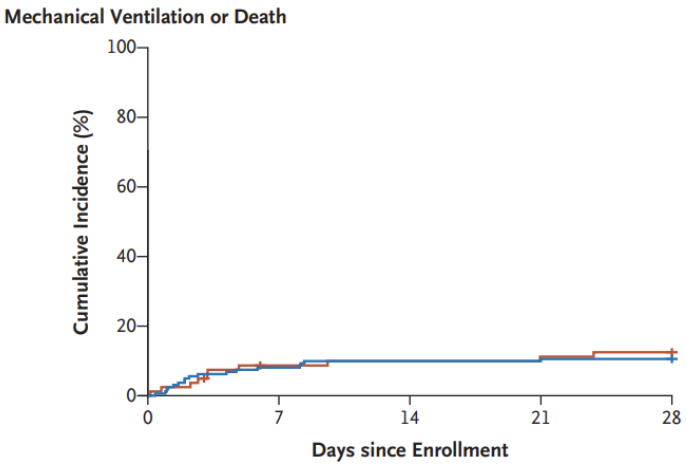
Gupta S et al. Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19. JAMA Intern Med. Published online October 20, 2020.

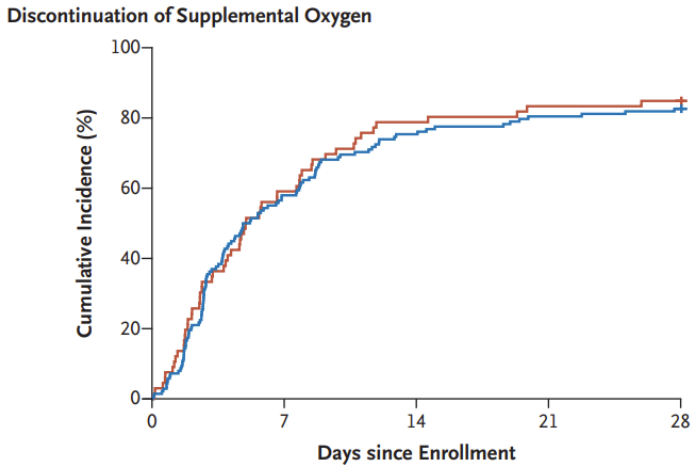
ORIGINAL ARTICLE

Efficacy of Tocilizumab in Patients Hospitalized with Covid-19

October 21, 2020

- 243 hospitalized patients with hyperinflammatory states in 7 Boston hospitals
- Randomized 2:1 to tocilizumab versus placebo
- Not effective in preventing death, intubation, or clinical worsening
- Results confirmed with two additional recent negative RCTs





Stone JH et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020 Oct 21. doi: 10.1056/NEJMoa2028836.

Hydroxychloroquine?

- Initially favored as a potential treatment due to dual anti-inflammatory properties and in vitro antiviral activity
- Was widely prescribed early in the pandemic
- Initial results were not promising, but there was a lack of clinical trial data for hospitalized patients

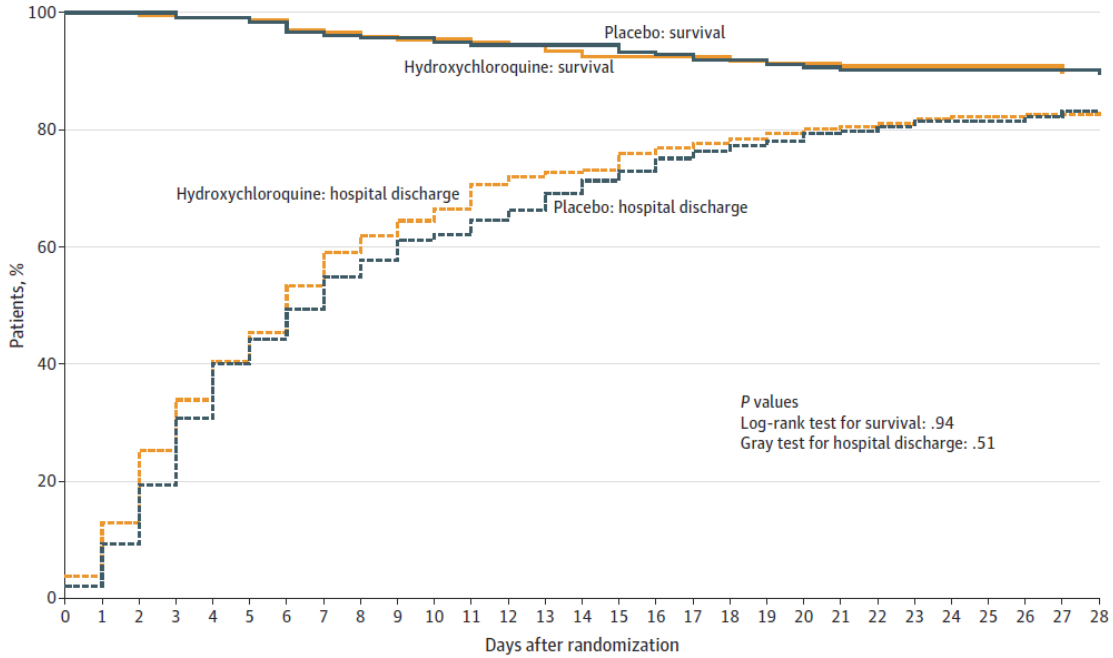
JAMA | Original Investigation

Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19

A Randomized Clinical Trial

November 9, 2020

- 479 hospitalized adults across 34 hospitals in the US
- Randomized to hydroxychloroquine or placebo
- No significant change in clinical status



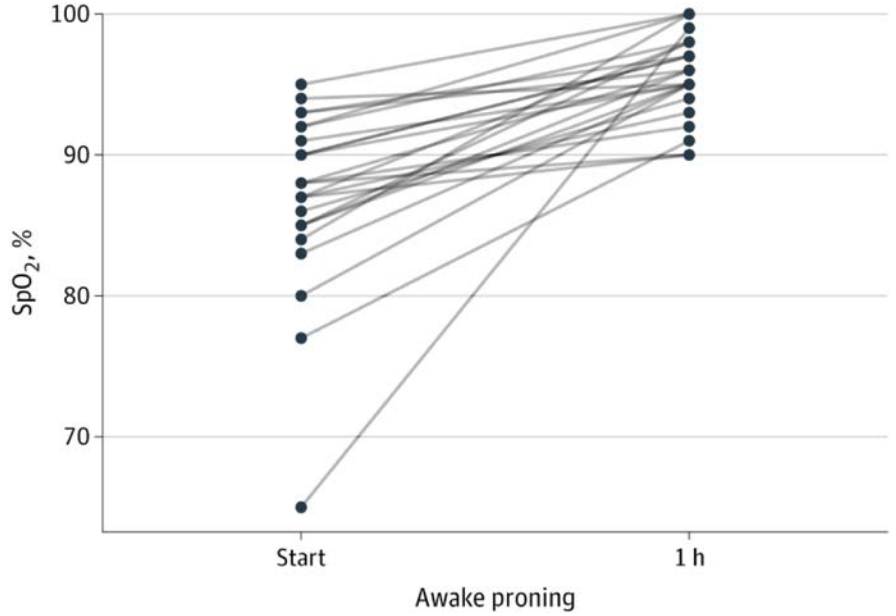
Self WH et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19. JAMA. Published online November 9, 2020.

Research Letter

June 17, 2020

Prone Positioning in Awake, Nonintubated Patients With COVID-19 Hypoxemic Respiratory Failure

- Among 29 hospitalized patients with severe disease, awake prone positioning was attempted
- 25/29 were able to maintain prone position for at least 1 hour
- SpO2 increased with prone positioning



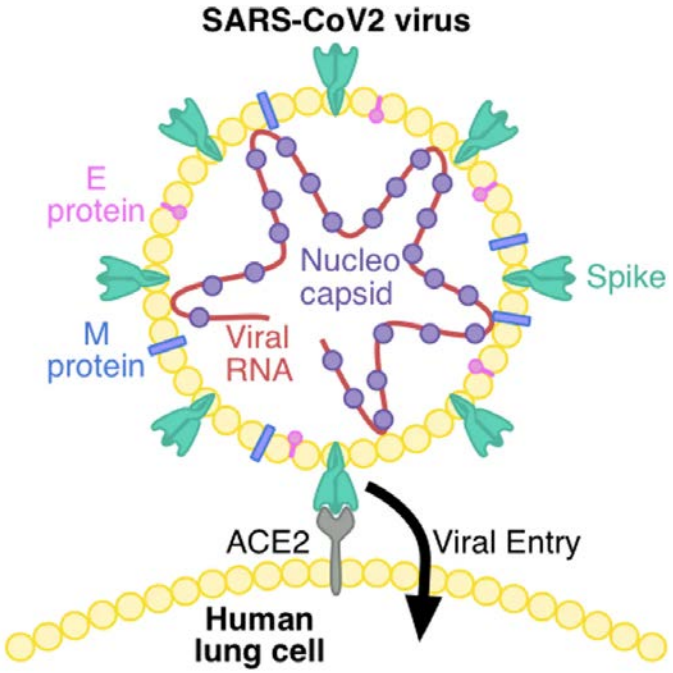
Thompson AE et al. Prone Positioning in Awake, Nonintubated Patients With COVID-19 Hypoxemic Respiratory Failure. JAMA Intern Med. 2020;180(11):1537-1539.

Treatment summary

- More RCT data is guiding therapy, improving treatment decisions
- No game changing therapies yet
  - Mostly hope for improving / shortening symptoms
- Remdesivir shortens time to recovery and trend towards decreased mortality, better results when used early in severe infection
- Monoclonal antibodies have promising early data for mild-moderate infections, more to come
- Dexamethasone has mortality benefit, better results when used in severe / critical illness
- Adequate supportive care remains the bedrock of treatment
  - And sometimes prone positioning can help in a pinch

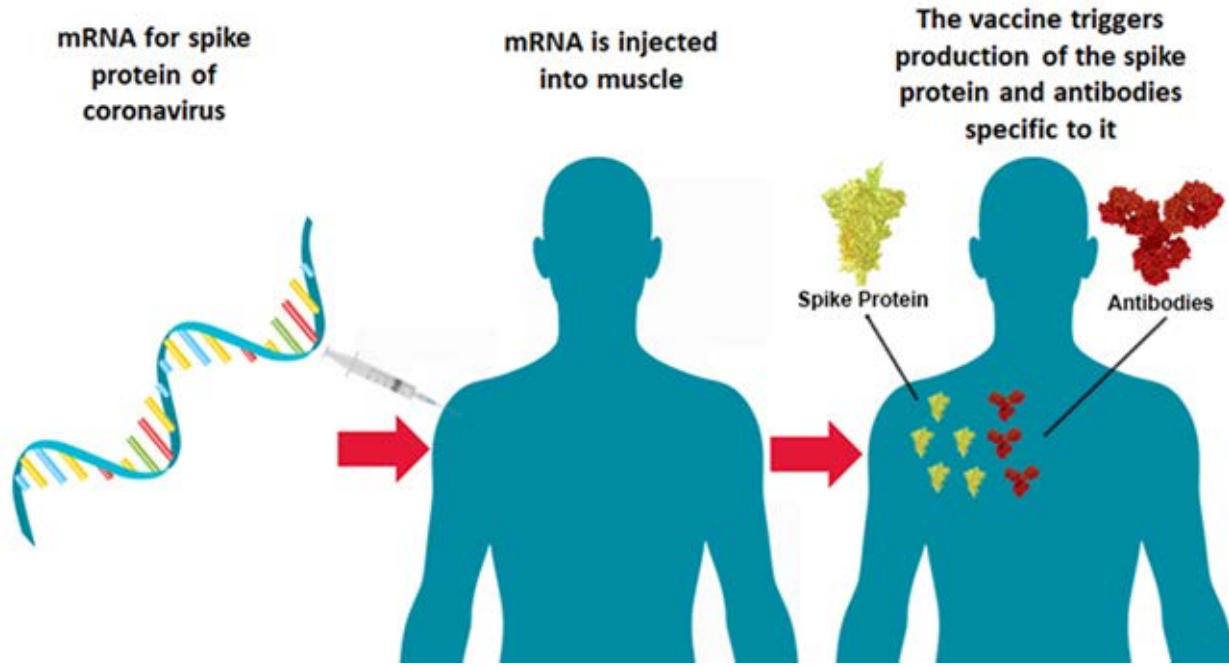
Vaccine updates

Vaccine development



- Vaccines typically take years-decades to develop
- Currently have >11 vaccines in phase III trials
- All target the viral spike glycoprotein antigen
  - Inhibits replication in vitro and prevents infection in cell culture
- Many are RNA / DNA vaccines
  - Some viral protein, some viral vector, some inactivated / attenuated

mRNA vaccines



- First of its kind
- mRNA injected into muscle
- Muscle cells produce spike protein
- Thought to improve T cell response to vaccine
- However mRNA is unstable and requires ultra cold temperatures and a very good cold chain
- Early data is rolling in…

PFIZER AND BIONTECH ANNOUNCE VACCINE CANDIDATE AGAINST COVID-19 ACHIEVED SUCCESS IN FIRST INTERIM ANALYSIS FROM PHASE 3 STUDY

Monday, November 09, 2020 - 06:45am

- 43,538 participants
  - Two dose series of mRNA vaccine
- No serious safety concerns
- First planned interim analysis at 94 patients reveals 90% effectiveness
  - In preventing infection
- Trial will run until 164 confirmed cases are documented
- Submission for EUA planned after the two-month safety milestone required by FDA, in the third week of November

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against

Timing

- Pfizer estimates it could have 30 to 40 million doses of the vaccine before the end of the year
  - Enough for 15 to 20 million people (2-dose series)
- Silver lining of rising cases is that many more vaccine trials will be reporting results soon
  - Many testing similar mRNA technology that is likely to have similar efficacy
- This will boost supply, but initial approved doses will require rationing

Fairly Prioritizing Groups for Access to COVID-19 Vaccines

September 10, 2020

Govind Persad, JD, PhD[1]; Monica E. Peek, MD, MPH, MS[2]; Ezekiel J. Emanuel, MD, PhD[3]

- Ethicist published a viewpoint on who should be prioritized for early vaccination
- Focus on principles of harm prevention and prioritizing the disadvantaged
  - Healthcare workers (50%)
  - People in high-risk occupations and housing (25%)
  - People with high-risk conditions (25%)
- Within each category, early preference should be given to individuals with high-risk conditions

Persad G et al. Fairly Prioritizing Groups for Access to COVID-19 Vaccines. JAMA. 2020;324(16):1601-1602.

Preventing the Spread of SARS-CoV-2 With Masks and Other "Low-tech" Interventions

Andrea M. Lerner, MD, MS[1]; Gregory K. Folkers, MS, MPH[1]; Anthony S. Fauci, MD[1]

October 26, 2020

- Low-tech interventions are successful
  - Masking
  - Social distancing
  - Hand hygiene
  - Prompt testing
- "it must be emphasized that these [low-tech] interventions will still be needed after a vaccine is available"

Lerner AM et al. Preventing the Spread of SARS-CoV-2 With Masks and Other "Low-tech" Interventions. JAMA. Published online October 26, 2020.

Vaccine summary

- Many companies are working on phase III trials of vaccines
- Preliminary results from mRNA vaccines are promising for preventing infections
- Vaccines are coming soon
  - Pfizer EUA application expected next week
- Triage and distribution will be ethically challenging
- Arrival of vaccines is not a signal to stop our other interventions
- Time will provide more information about the durability and effectiveness of these therapies

Coagulopathy

COVID-19 induced coagulopathy

- Commonly presents with marked elevation of D-dimer with modest increase in PT/PTT
- Appears to be distinct from conventional sepsis induced coagulopathy
- Associated with micro and macrovascular thrombosis and organ failure
- Many studies demonstrate increased VTE risk
  - 3.3-6.4% of ward patients
  - 16.7-47% of ICU patients
- It is unclear what role empiric anticoagulation should play in treatment

Hadid T et al. Coagulation and anticoagulation in COVID-19. Blood Rev. 2020 Oct 8 : 100761.

ORIGINAL ARTICLE

jth

Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy

24 March 2020

- Retrospective review of 449 patients with severe infection at one hospital in Wuhan, China
  - 99 received heparin for 7 days or longer
  - No specific inclusion / exclusion criteria had been established
  - Mostly prophylactic dosing, which is not standard of care in China
- No difference in 28-day mortality between heparin users and non-users (30.3% vs 29.7%)
- If D-dimer was >6x ULN, there was a mortality benefit (32.8% vs 52.4%)
- First signal that increased anticoagulation dose may be beneficial

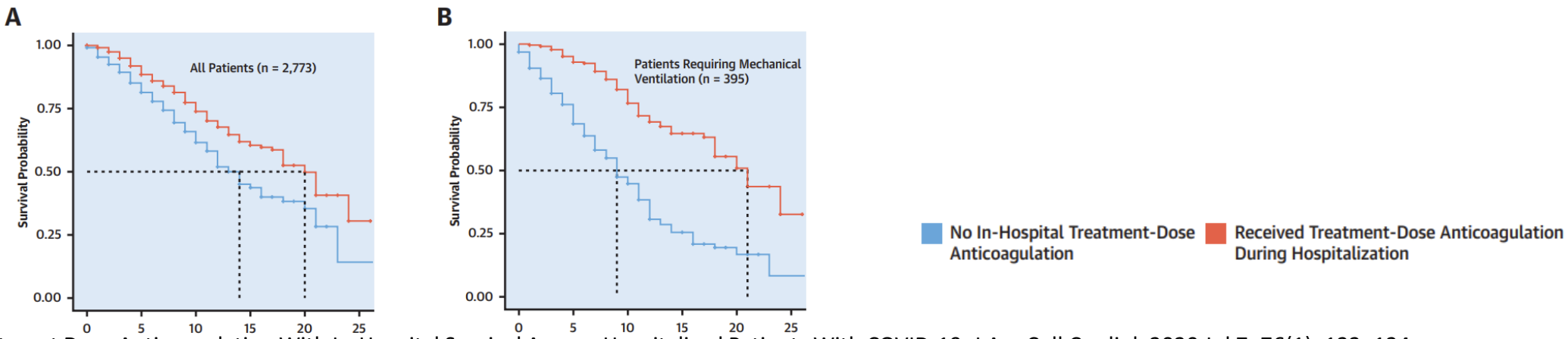
Tang N et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020 May;18(5):1094-1099.

Letters

Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19

7 July 2020

- Retrospective review of 2773 hospitalized patients in one academic health center in NY
  - 28% received therapeutic anticoagulation
  - No protocol in place, but patients who received AC were more likely to be intubated or have elevated D-dimer
- In hospital mortality was similar (22.5% vs 22.8%)
- Median survival was longer in the AC group (21 days vs 14 days)
- No significant difference in major bleeding rate (3% vs 1.9%)



Paranjpe I et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. J Am Coll Cardiol. 2020 Jul 7; 76(1): 122–124.

Where we are now

- Based on this data, many guidelines advocated for increased anticoagulation in patients admitted with COVID infection
  - Some based on D-dimer
  - Some based on severity of illness
- However, this is just retrospective data
  - Many RCTs in similar conditions have not shown a clinical benefit for increased anticoagulation
- And may be exposing patients to significant risk
  - One retrospective study of critically ill COVID patients reported 21% of patients had major hemorrhage when using increased anticoagulation protocols
- RCTs are underway to better elucidate best practices

Fraisse M et al. Thrombotic and hemorrhagic events in critically ill COVID-19 patients: a French monocenter retrospective study. Crit Care. 2020 Jun 2;24(1):275.
Chowdhury JF et al. Anticoagulation in Hospitalized Patients with Covid-19. N Engl J Med 2020; 383:1675-1678.

Waning immunity and reinfection

Alaska News

This Alaskan got COVID-19 and recovered. Four months later, she got infected again - and felt much worse.

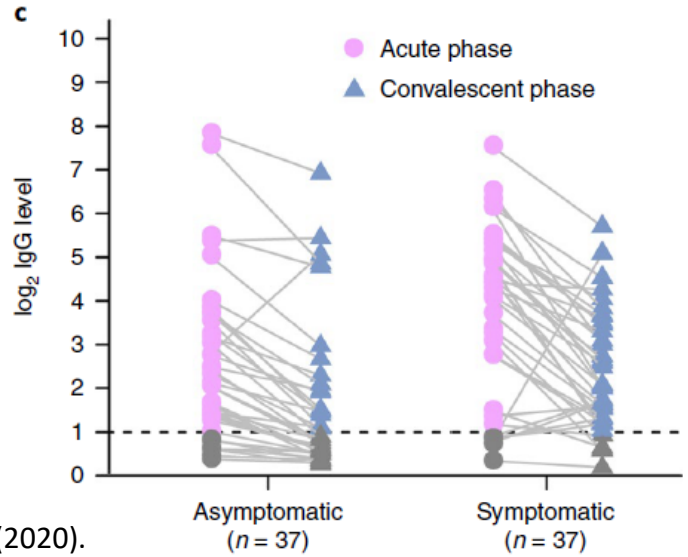
Author: Annie Berman Updated: 1 day ago Published 1 day ago

Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections

nature medicine

18 June 2020

- 37 asymptomatic patients compared with 37 age/sex matched symptomatic patients in China
- Antibodies were higher in the symptomatic group
- 95% of patients had a decrease in antibody levels at 2-3 months
- 40% of asymptomatic patients were seronegative at 2-3 months
  - Compared to 12.9% of symptomatic patients
- Rate of decay was not calculated

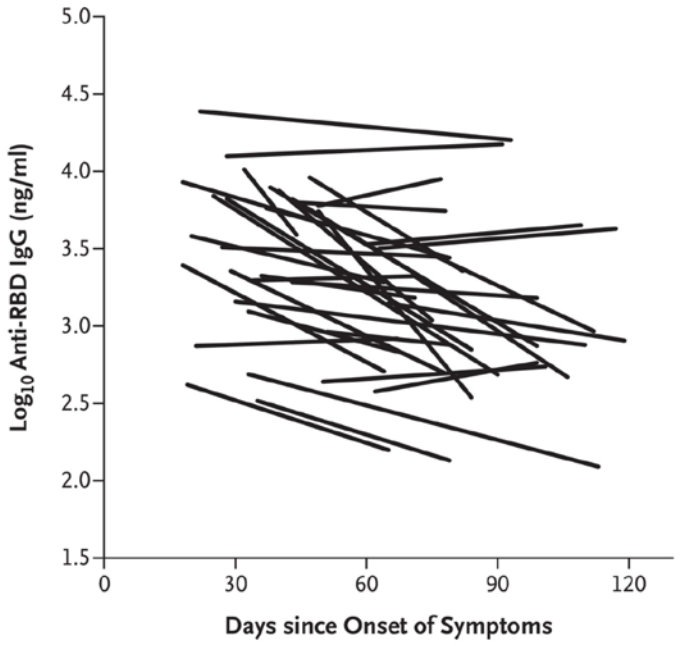


Long QX et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nature Medicine volume 26, pages 1200–1204(2020).

Rapid Decay of Anti–SARS-CoV-2 Antibodies in Persons with Mild Covid-19

SEPTEMBER 10, 2020

- 34 patients with history of mild infection underwent serial antibody titer testing
  - 31 had two measurements, 3 had three measurements
- Overall, antibodies were found to have a half life of ~36 days
  - 95% CI 26-60 days



Ibarrondo FJ et al. Rapid Decay of Anti–SARS-CoV-2 Antibodies in Persons with Mild Covid-19. N Engl J Med 2020; 383:1085-1087.

Coronavirus Disease 2019 (COVID-19) Re-infection by a Phylogenetically Distinct Severe Acute Respiratory Syndrome Coronavirus 2 Strain Confirmed by Whole Genome Sequencing

August 25, 2020.

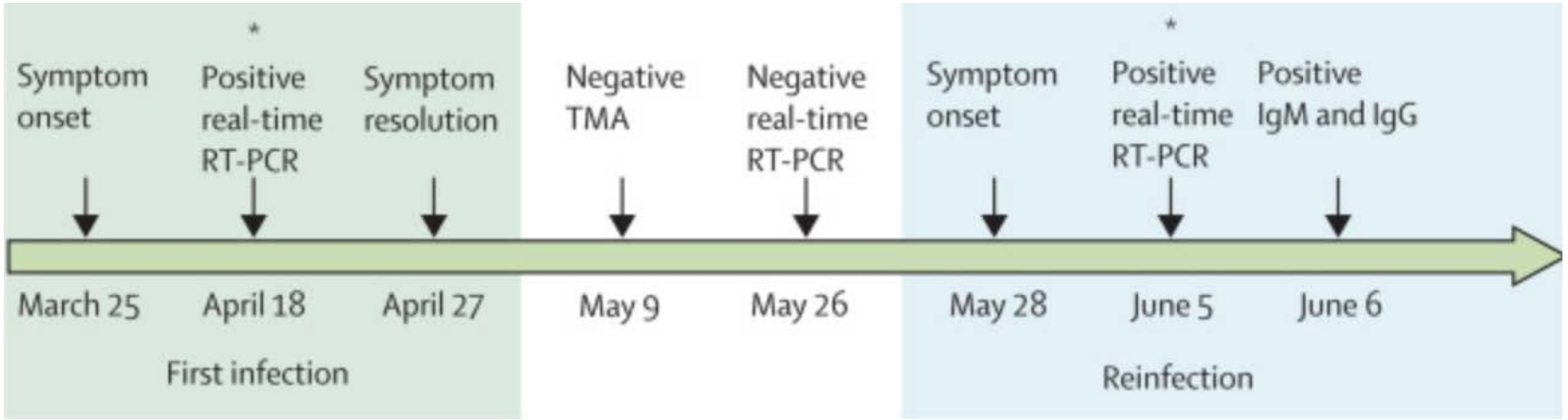
- 33-year-old found to have asymptomatic infection 142 days after their first symptomatic episode
  - Previously healthy, immunocompetent
  - Second episode was noted during airport screening
- Serologies were negative upon presentation to the hospital, and converted positive on day 3
- Genome analysis confirmed it was a different lineage of SARS-CoV-2

To KK et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. Clin Infect Dis. 2020 Aug 25;ciaa1275.

Genomic evidence for reinfection with SARS-CoV-2: a case study

October 12, 2020

- 25-year-old found to have symptomatic infection 48 days after their first symptomatic episode
  - Previously healthy, immunocompetent
  - Increased severity of the second episode with hypoxia
- Genome analysis confirmed it was a different lineage of SARS-CoV-2



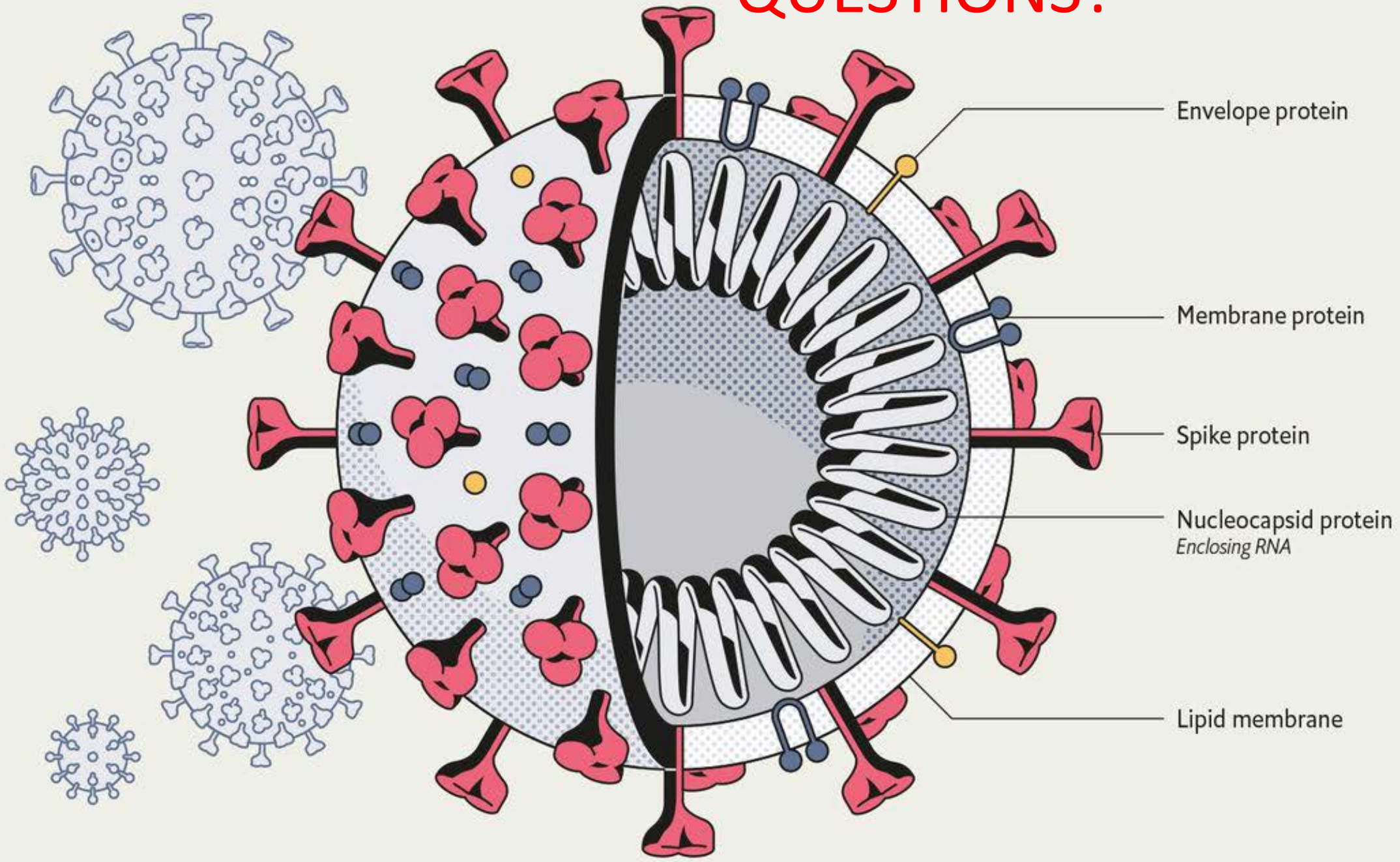
Tillet RL et al. Genomic evidence for reinfection with SARS-CoV-2: a case study. Lancet Infect Dis. 2020 Oct 12.

CDC Guidelines for re-testing

- Patients are very unlikely to be reinfected within 12 weeks of initial COVID infection, therefore if exposed but asymptomatic they should not be tested (any positive test is likely continued shedding)
  - If a patient is symptomatic with no other clinical explanation, then re-testing should be done with guidance of experts
- After 90 days, patients recovered from COVID appear to be susceptible to reinfection

https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html

QUESTIONS?


Envelope protein
Membrane protein
Spike protein
Nucleocapsid protein
Enclosing RNA
Lipid membrane

CDC Guidelines for isolation

- Duration of isolation and precautions
  - For most patients, isolation and precautions can be discontinued 10 days after symptom onset if afebrile for >24 hours and improving symptoms; or if asymptomatic, 10 days after 1st positive SARS-CoV2 test
    - Evidence shows that even though viral RNA may persist in upper respiratory system, replication-competent virus has not been detected >10 days from disease onset in mild-moderate (and most severe) COVID patients
  - A limited number of persons with severe illness may produce replication-competent virus beyond 10 days that may warrant extending isolation and precautions for up to 20 days after symptom onset, particularly if immuncompromised
  - A test based strategy is no longer recommended to discontinue isolation unless trying to discontinue precautions prior to 10 days
    - Exception is in patients who are severely immunocompromised, in consult with ID experts

Change in Antibodies to SARS-CoV-2 Over 60 Days Among Health Care Personnel in Nashville, Tennessee

September 17, 2020

- Study of 249 health care employees with direct contact with patients with COVID-19
  - 19 (7.9%) with positive antibodies at baseline
- 11 (58%) of these participants had negative serology at 60 day follow up
  - 5 reported symptoms before baseline serology
  - 6 were asymptomatic
- The other 8 participants had decreased antibody titers
  - 6 reported symptoms before baseline serology
  - 2 were asymptomatic

Patel MM et al. Change in Antibodies to SARS-CoV-2 Over 60 Days Among Health Care Personnel in Nashville, Tennessee. JAMA. 2020;324(17):1781-1782..