COVID-19 Treatment Update

Jessica Cataldi MD, MSCS
Pediatric Infectious Diseases
University of Colorado
@jesscataldi

1

1

Disclosures / COI

I am on the board of directors for Immunize Colorado

I will briefly mention one paper my husband wrote

I have no financial conflicts to disclose

2

2

Objectives

Describe evidence-based treatments for COVID-19

- Identify resources for treatment guidance
- Review evidence for COVID-19 treatments with a focus on hospitalized patients
- Learn recommended treatments for patients at different stages of disease / severity of illness
- Review some treatments that are NOT recommended

3

3

Resources

NIH and **IDSA** both maintain frequently updated treatment guidelines with summaries of the evidence

JPIDS has some pediatric-focused publications, but most that reference treatment approaches are out of date

Children's Hospital Colorado COVID19 clinical pathways and guidance site includes an acute COVID19 pathway that is being revised this month

https://www.covid19treatmentguidelines.nih.gov/, https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/, https://academic.oup.com/jpids/pages/covid-19-special-issue, https://www.childrenscolorado.org/health-professionals/coronavirus-professional-resources/clinical-guidance-practice-resources/covid19-clinical-pathways/

4

Viewpoint https://jamanetwork.com/journals/jama/fullarticle/2763802

March 24, 2020

Treating COVID-19—Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics

Andre C. Kalil, MD, MPH[1]
Author Affiliations | Article Information
JAMA. 2020;323(19):1897-1898. doi:10.1001/jama.2020.4742

In the 2014 Ebola outbreak, close to 30 000 individuals developed Ebola viral disease (EVD), and numerous therapies were tested against this virus, including chloroquine, hydroxychloroquine, favipiravir, brincidofovir, monoclonal antibodies, antisense RNA, and convalescent plasma, among many others. With such a large number of therapeutic interventions given to affected patients, the goal was to determine which was efficacious against Ebola. Ultimately, none proved to be efficacious or safe.

Why were new therapies not discovered? One reason is because virtually all studies were single-group interventions without concurrent controls, which led to no definitive conclusion related to efficacy or safety. Despite much resistance and controversy regarding asking patients with EVD to participate in a randomized clinical trial (RCT),[1] the National Institutes of Health (NIH) conducted the first and only RCT during that outbreak. It took several months to design the trial, but it was implemented and successfully launched during the outbreak; however, it was too late for the RCT to be completed.[2] This tragedy of not discovering new therapies during an outbreak cannot be repeated.

5

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The world is now facing a pandemic of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2, the cause of COVID-19), for which no proven specific therapies are available, other than supportive care. In China, and now Italy, France, and Spain, a large number of patients have received off-label and compassionate use therapies such as chloroquine, hydroxychloroquine, azithromycin, lopinavir-ritonavir, favipiravir, remdesivir, ribavirin, interferon, convalescent plasma, steroids, and anti–IL-6 inhibitors, based on either their in vitro antiviral or anti-inflammatory properties. These therapies have been mostly given without controls, except for a few randomized trials started in China, and more recently in the US.[3]

6

Viewpoint

https://jamanetwork.com/journals/jama/fullarticle/2763802

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A control group may be defined as the standard of care with or without placebo. One concern during epidemics, for example, during the 2014 Ebola outbreak (and the current COVID-19 pandemic), is whether it is ethical to give patients a placebo. If the disease is not 100% lethal and it is not known whether the experimental drug would help or harm a patient (ie, a situation with true equipoise), then it is ethical to conduct an RCT. Without a control group, it is not possible to accurately determine the harms of any experimental drug. In reality, the placebo group will always be safer (regarding adverse effects) than the experimental group because patients in the placebo group will receive the established standard of care. In contrast, compared with RCTs, the administration of old or new drugs (eg, off-label use, compassionate use, single-group cohorts, case-historical controls, clinical trials without controls) may be less safe, and moreover, will not lead to the discovery of any new therapy.

In addition to the risk of harming patients without the possibility to even detect the magnitude of harm, the administration of off-label drug use, compassionate drug use, and uncontrolled studies during a pandemic also could discourage patients and clinicians from participating in RCTs, hampering any knowledge that could be gained about the effects of the drug being tested. More than 300 000 individuals have been diagnosed with COVID-19; however, just a few hundred have been offered participation in RCTs. Meanwhile, many more patients have been offered uncontrolled drugs.

7

At the Center of a Storm: The Search for a Proven Coronavirus Treatment

Taking an experimental drug can be worse than taking nothing at all, warns Dr. Andre Kalil: "You are treating emotion."

Dr. Andre Kalil, an infectious diseases and intensive care specialist at the University of Nebraska Medical Center in Omaha, is a principal investigator in a major trial of a drug to treat Covid-19.

8

8

Why trials matter: convalescent plasma

https://www.nature.com/articles/s41591-021-01488-2

nature medicine ARTICLES

OPEN

Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial

Philippe Bégin, Jeannie Callum, Erin Jamula, Richard Cook, Nancy M. Heddle

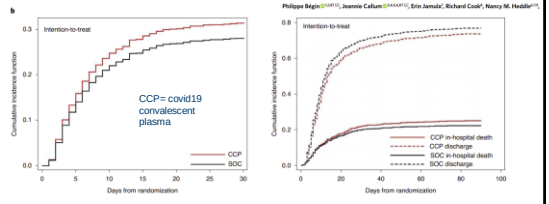

Fig. 2 | Study outcomes. a. Patient outcomes for the primary and secondary endpoints. **b.** Cumulative incidence functions of the primary outcome

9

9

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78% of planned enrollment after meeting stopping criteria for futility. In total, 940 patients were randomized, and 921 patients were included in the intention-to-treat analysis. Intubation or death occurred in 199/614 (32.4%) patients in the convalescent plasma arm and 86/307 (28.0%) patients in the standard of care arm—relative risk (RR) = 1.16 (95% confidence interval (CI) 0.94–1.43, P = 0.18). Patients in the convalescent plasma arm had more serious adverse events (33.4% versus 26.4%; RR = 1.27, 95% CI 1.02–1.57, P = 0.034). The antibody content significantly modulated the therapeutic effect of convalescent plasma. In multivariate analysis, each standardized log increase in neutralization or antibody-dependent cellular cytotoxicity independently reduced the potential harmful effect of plasma (odds ratio (OR) = 0.74, 95% CI 0.57–0.95 and OR = 0.66, 95% CI 0.50–0.87, respectively), whereas IgG against the full transmembrane spike protein increased it (OR = 1.53, 95% CI 1.14–2.05). Convalescent plasma did not reduce the risk of intubation or death at 30 d in hospitalized patients with COVID-19. Transfusion of convalescent plasma with unfavorable antibody profiles could be associated with worse clinical outcomes compared to standard care.

10

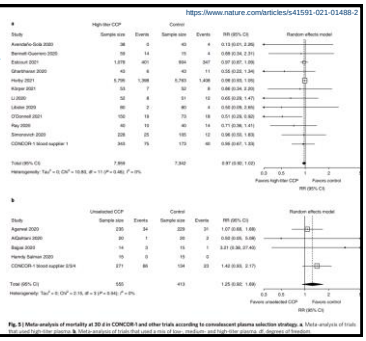
10

Why trials matter: convalescent plasma

https://www.nature.com/articles/s41591-021-01488-2

Meta-analysis of convalescent plasma trials fails to show significant benefit for high-titer (a) or low/medium/mixed-titer plasma (b)

Prior US plasma study without control group showed high titer associated with better outcomes than low titer:
high-titer CCP> low-titer CCP



11

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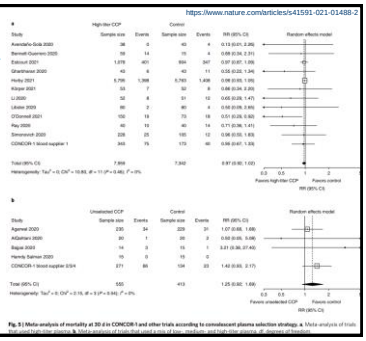
Why trials matter: convalescent plasma

https://www.nature.com/articles/s41591-021-01488-2

This RCT: control group and ability to stratify analysis by immune characteristics of plasma shows high neutralization titer caused less harm but was not superior to control:
control ≥ high-titer CCP > low-titer CCP

Without RCT w control group, only see part of the picture



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12

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html
https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/

Caveats on our discussion today (data as of mid-Sept 2021)

Despite

somewhere between 5 and 25 million children diagnosed with COVID19 in the US,
between 40,000 and 250,000 pediatric COVID19 hospitalizations in the US,
and ~500 children with COVID19 who have died in the US,

most of what I will present today is the evidence and guidance for treatment in adults.

In some ways, this may be ok for adolescent patients who share physiology that is closer to adults. Also note adolescents requiring critical care for severe COVID-19 may have more 'adult' comorbidities like obesity, obstructive sleep apnea, risk for blood clots.

Most of this evidence comes from immense collaborative effort of multi-site RCTs from the UK (RECOVERY), WHO (Solidarity), Canada (REMAP-CAP), and some from NIH group here in the US (ACTT1-4).

13

13

Children's Hospital Colorado data March-July 2020

- Comparing 66 children with COVID-19 admitted to the hospital and 369 with COVID-19 not admitted, these factors were associated with hospitalization:
  - Age<3 months or >20 years
  - Larger household size
  - Obesity
  - Breathing conditions (asthma and sleep apnea)
  - Gastrointestinal diseases
  - Diabetes
  - Neurologic condition
  - Immune-compromise
  - Preterm birth

Graff, K, *et al.* "Risk Factors for Severe COVID-19 in Children" *PIDJ*, 2021

14

Pediatric COVID-19 hospitalizations

- Since then, have had many more children sick with COVID-19: ~1200 pediatric COVID-19 hospitalizations to date in Colorado (AAP/CHA)
- As more adults are protected by vaccination, proportionally more cases occur among children
- As Delta is more contagious and causes more severe disease, it takes a smaller initial number of cases to spread twice as quickly and then make 1.5-2.5x more of the infected people severely ill- this includes among kids

https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/

15

Pediatric COVID19 hospitalizations

ONLINE FIRST SEPTEMBER 15, 2021—ORIGINAL RESEARCH

Factors Associated With COVID-19 Disease Severity in US Children and Adolescents

James W Antoon, MD, PhD[a], Carlos G Grijalva, MD, MPH[b], Cary Thurm, PhD[c], Troy Richardson, PhD[c], Alicen B Spaulding, PhD, MPH[d], Ronald J Teufel II, MD, MSCR[e], Mario A Reyes, MD[a], Samir S Shah, MD[a], Julianne E Burns, MD[a], Chen C Kenyon, MD, MSHP[a], Adam L Hersh, MD, PhD[a], Derek J Williams, MD, MPH[f]

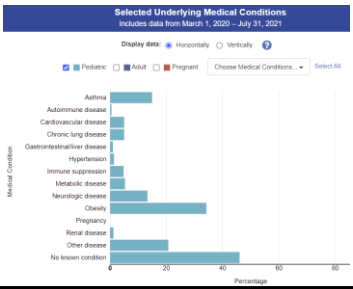
- Retrospective cohort study across 45 US children's hospitals April-September 2020
- ~20,000 COVID19 encounters, 80% of these discharged from ED
- Hospitalizations: 79% moderate, 11% severe and 9% very severe disease
- Factors associated with hospitalization: obesity / type 2 DM, immunocompromised, pulmonary disease, cardiovascular disease, neurologic disease, asthma
- Factors associated with severe hospitalization: cardiovascular disease, pulmonary disease, age>4 years, obesity / type 2 DM, neurologic disease

https://www.journalofhospitalmedicine.com/jhospmed/article/245964/hospital-medicine/factors-associated-covid-19-disease-severity-us-children?channel=28090

16

https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network

National COVID-NET data



46% of children hospitalized with COVID-19 **do not** have another condition

Although *some* of these are children with trauma or appendicitis incidentally found to have COVID-19, most have primary or secondary COVID-19 illness/complications

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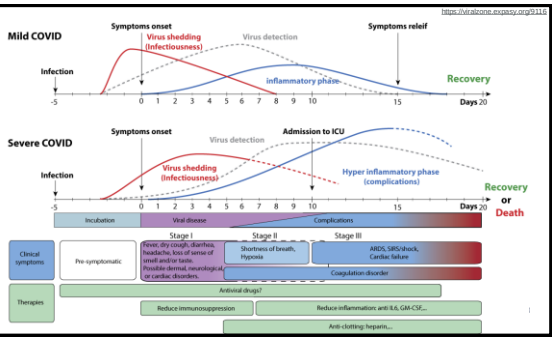
https://viralzone.expasy.org/9116

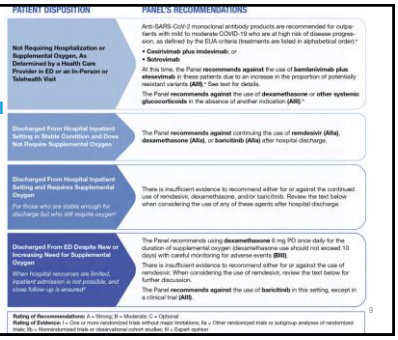


18

https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/

NIH Treatment Guidelines for COVID-19 in Adults not requiring hospital admission

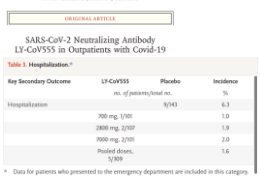
- High risk for severe disease: **monoclonal antibody** pre-emptive therapy
- **Steroids:**
  - Only use if sending home with oxygen / increased oxygen support from baseline
  - Also ok for non-hypoxemic patients with related indication (croup, asthma exacerbation)



19

https://www.nejm.org/doi/10.1056/NEJMoa2029849, https://www.medrxiv.org/content/10.1101/2021.05.19.21257469v2.full-text

Monoclonal antibodies: pre-emptive treatment

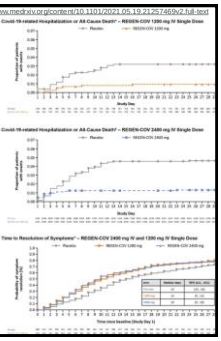

ORIGINAL ARTICLE

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

Table 3. Hospitalization.*

Key Secondary Outcome	LY-CoV555	Placebo	Incidence
	no. of patients/total no.		%
Hospitalization		9/143	6.3
	700 mg, 1/101		1.0
	2800 mg, 2/107		1.9
	7000 mg, 2/101		2.0
	Pooled doses, 5/309		1.6

* Data for patients who presented to the emergency department are included in this category.



Bamlanivimab and casirivimab-imdevimab as **early treatment** show reduction in quantity of virus in respiratory samples, reduced time to resolution of symptoms, and decreased risk of medically-attended covid19 outcomes (hospitalization, ED visit, +/-death)

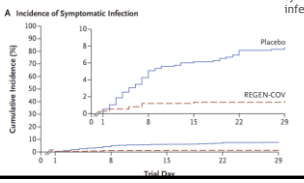
20

https://www.nejm.org/doi/full/10.1056/NEJMoa2109682

Monoclonal antibodies: post-exposure prophylaxis


ORIGINAL ARTICLE

Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19



Participants with Symptomatic Infection

	no. (%)
Placebo	59 (7.8)
REGEN-COV	11 (1.5)

Relative risk reduction, 81.4%

Odds ratio, 0.17 (95% CI, 0.09–0.33)
P<0.001

Casirivimab-imdevimab given as **post-exposure prophylaxis** among general sample (31% had high risk for severe COVID19) showed reduction in risk of symptomatic infection plus decreased quantity of virus in respiratory samples and decreased symptom duration for those who did develop infection

21

https://academic.oup.com/jpids/article/10/5/629/6060076

Monoclonal antibodies and kids

Initial Guidance on Use of Monoclonal Antibody Therapy for Treatment of Coronavirus Disease 2019 in Children and Adolescents

Joshua Wolf, Mark J Abzug, Rachel L Wattier, Paul K Sue, Surabhi B Vora, Philip Zachariah, Daniel E Dulek, Alpana Waghmare, Rosemary Olivero, Kevin J Downes ... Show more

Journal of the Pediatric Infectious Diseases Society, Volume 10, Issue 5, May 2021, Pages 629–634, https://doi.org/10.1093/jpids/piaa175

Published: 03 January 2021 **Article history**

Conclusions

Based on evidence available as of December 20, 2020, the panel suggests against routine administration of monoclonal antibody therapy (bamlanivimab, or casirivimab and imdevimab), for treatment of COVID-19 in children or adolescents, including those designated by the FDA as at high risk of progression to hospitalization or severe disease. Clinicians and health systems choosing to use these agents on an individualized basis should consider risk factors supported by pediatric-specific evidence and ensure the implementation of a system for safe and timely administration that does not exacerbate existing healthcare disparities.

This guidance from January 2021 is being revised and likely to be more favorable toward recommending use of monoclonal antibodies for COVID19 treatment and prevention among children with risk factors

Challenges:

- Lack of pediatric-specific data on efficacy
- Lower quality pediatric data to identify risk factors for severe COVID19
- Even adult studies used general sample, so hard to estimate effect size / NNT for high-risk patients

22

22

https://covid19.colorado.gov/for-coloradans/covid-19-treatments

I am a provider and I want to prescribe monoclonal antibody treatment for my patient. How do I do that?

COLORADO
Department of Public Health & Environment

STEP ONE

Determine that your patient meets the eligibility criteria to receive the product.

Eligible patients for monoclonal antibody treatments for people infected with COVID-19 are:

1. Adults and pediatric patients (age 12-17 years and weighing at least 40 kg)
2. Symptomatic with less than 10 days since symptom onset AND
3. At high risk.
   - The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:
     - Older age (≥65 years).
     - Obesity or being overweight (for example, adults with BMI >25 kg/m² https://www.cdc.gov/growthcharts/clinical_charts.htm, or if age 12-17, have BMI ≥85th percentile for their age and gender-based on CDC growth charts).
     - Pregnancy.
     - Chronic kidney disease.
     - Diabetes.
     - Immunosuppressive disease or immunosuppressive treatment.
     - Cardiovascular disease (including congenital heart disease) or hypertension.
     - Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension).
     - Sickle cell disease.
     - Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies).
     - Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation not related to COVID-19).

Eligibility:

- Positive COVID19 test or exposed
  AND
- ≥ 12 years of age
  AND
- ≥ 40kg
  AND
- Has risk factor for severe COVID19

23

23

https://covid19.colorado.gov/for-coloradans/covid-19-treatments
https://cdphe.redcap.state.co.us/surveys/?s=PX9LW9CEE

COLORADO
Department of Public Health & Environment

COVID-19 Monoclonal Antibody Connector Tool

If you have more than one patient to submit for the medication, each time you submit the COVID-19 Monoclonal Antibody Connector Form you will be given the opportunity to **download a PDF** of the data you provided. For confidentiality reasons we are unable to send the PDF via email.

Please note that once you submit a form you cannot return to edit it. **Do not use your browser's back button as this will require you to start over with the public link.**

Next Page >>

- Ok to use in vaccinated patients
- Should defer subsequent COVID19 vaccine doses for 90 days (concern for reduced effectiveness if given earlier)
- Adverse events: infusion reactions

What are these monoclonals anyway?

- Synthetic antibodies to spike protein - different products target different spike domains
- Certain SARSCOV2 variants render certain monoclonals inactive (for example bamlanivimab not active against beta, gamma, or iota)
- FDA updates product licensure and use based on regional variant patterns over time

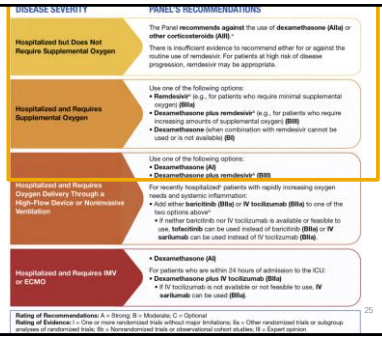
24

24

https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/

NIH Treatment Guidelines for COVID-19 in Hospitalized Adults

- Requiring O2: **remdesivir +/- steroids**
- High-flow/NIPPV: **steroids +/- remdesivir**
  - Recently hospitalized, escalating resp support, with systemic inflammation: add **baricitininib** or **tocilizumab**
- Intubated/ECMO: **steroids**
  - Recent ICU arrival, escalating support, systemic inflammation: add **tocilizumab**



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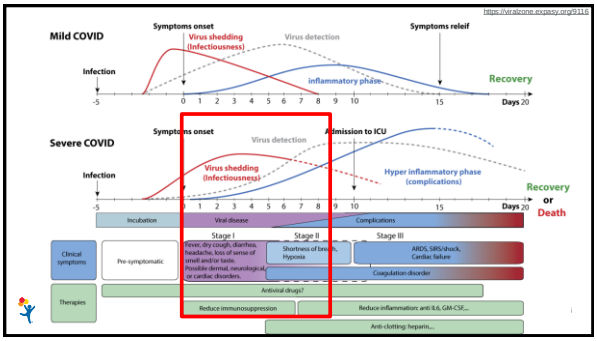
https://viralzone.expasy.org/9116



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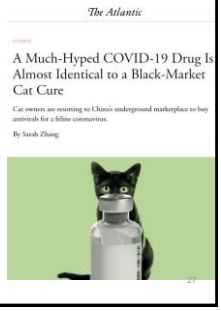
https://www.covid19treatmentguidelines.nih.gov/
https://www.theatlantic.com/science/archive/2020/05/remdesivir-cats/611341/

Remdesivir

- Intravenous antiviral
- Nucleotide adenosine analog: binds to SARSCOV2 viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription (acts kind of like NRTI HIV drugs)
- Adverse effects:
  - Nausea, GI upset
  - Elevated AST/ALT, less commonly PT prolongation
  - Monitor hepatic function closely, consider stopping if >?10x ULN (or maybe before then)
- Note on renal insufficiency:
  - Cyclodextrin compound (SBECD) used to stabilize / improve solubility of remdesivir (also used with voriconazole)
  - If eGFR<30mL/min, can have increased accumulation of SBECD with resulting liver and kidney toxicity



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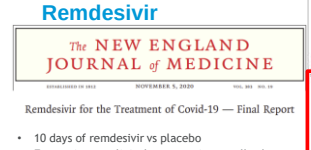
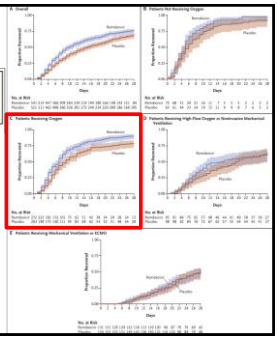
https://www.nejm.org/doi/full/10.1056/NEJMoa2021436

Remdesivir



Remdesivir for the Treatment of Covid-19 — Final Report

- 10 days of remdesivir vs placebo
- Faster time to clinical recovery in overall cohort, driven by benefit in patients on O2
- No significant difference in subgroup analyses for patients not on O2, patients on high-flow/NIPPV, or patients receiving mechanical ventilation/ECMO
- Significant improvement for patients starting treatment at <10 days from symptom onset



28

https://jamanetwork.com/journals/jama/fullarticle/2769871

Remdesivir

JAMA Network

QUESTION Does remdesivir provide a benefit on clinical status for patients hospitalized with moderate COVID-19 pneumonia?

CONCLUSION This clinical trial found that hospitalized patients with moderate COVID-19 randomized to a 5-day course, but not a 10-day course, of remdesivir had a statistically significant better clinical status vs standard care at 11 days, but the difference was of uncertain clinical importance.

POPULATION

357 Men
227 Women

Patients hospitalized with moderate COVID-19 pneumonia (pulmonary infiltrates plus room air oxygen >94%)

Median age: 57 years

LOCATIONS

105 Hospitals in the United States, Europe, and Asia

INTERVENTION

596 Patients randomized
584 Patients analyzed

193 10-Day remdesivir IV remdesivir, 200 mg on day 1, followed by 100 mg/d

191 5-Day remdesivir IV remdesivir, 200 mg on day 1, followed by 100 mg/d

200 Standard care

PRIMARY OUTCOME

Clinical status on day 11 rated on a categorical scale (1 = death , 7 = discharged) reported as odds ratio (OR >1 indicates difference in clinical status toward category 7 for remdesivir)

FINDINGS

Clinical status on day 11

The difference in the primary outcome indicating better clinical status at day 11 was **statistically significant** for the 5-day remdesivir group compared with the standard care group:

OR = 1.65 (95% CI, 1.09 to 2.48), 5-day remdesivir vs standard care, P = .02

The difference in the primary outcome indicating better clinical status at day 11 was **not statistically significant** for the 10-day remdesivir group compared with the standard care group:

10-day remdesivir vs standard care, P = .18

Spinner CD, Gottlieb RL, Criner GJ, et al; for the GS-US-540-5774 Investigators. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA. Published online August 21, 2020. doi:10.1001/jama.2020.16349

29

Other studies (in addition to this one) do not show benefit for 10 days over 5 days

29

https://www.nejm.org/doi/full/10.1056/nejmoa2023184
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00485-0/fulltext

Remdesivir- counterpoint

- WHO RCT failed to show benefit for remdesivir in time to improvement or mortality
  - Also failed to show benefit for hydroxychloroquine, lopinavir, or interferon
- Multi-country RCT in Europe (DisCoVeRy) failed to show benefit for remdesivir in time to improvement or mortality
  - Median symptom duration at time of treatment was 9 days (IQR 7-12)
  - SOC included steroids for later study period
  - 23% received steroids in ACTT-1 (showed remdesivir benefit) and 40% received steroids in DisCoVeRY (did not show remdesivir benefit)
- Benefit, if present, is for decreasing viral replication
  - Consider use early in disease course
  - No evidence of benefit for patients receiving more respiratory support than nasal cannula O2
  - Might be useful for immune-compromised who cannot control viral replication

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial

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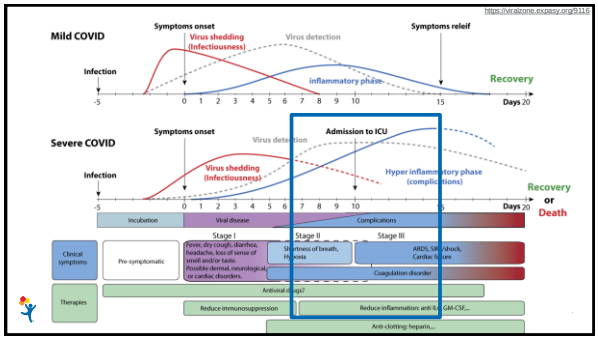
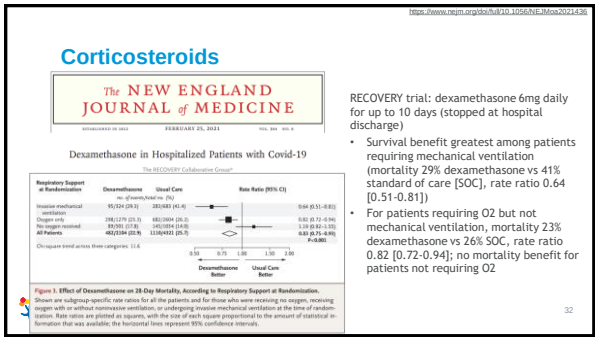

https://viralzone.expasy.org/9116
Mild COVID
Symptoms onset
Virus shedding (Infectiousness)
Virus detection
Symptoms releif
Infection
inflammatory phase
Recovery
Days
Severe COVID
Symptoms onset
Admission to ICU
Virus detection
Virus shedding (Infectiousness)
Infection
Hyper inflammatory phase (complications)
Recovery or Death
Days
Incubation
Viral disease
Complications
Stage I
Stage II
Stage III
Clinical symptoms
Pre-symptomatic
Fever, dry cough, diarrhea, headache, loss of sense of smell and/or taste. Possible dermal, neurological or cardiac disorders.
Shortness of breath, Hypoxia
ARDS, SIR/sShock, Cardiac failure
Coagulation disorder
Therapies
Antiviral drugs?
Reduce immunosuppression
Reduce inflammation: anti IL, GM-CSF...
Anti-clotting: heparin,...

31


https://www.nejm.org/doi/full/10.1056/NEJMoa2021436
Corticosteroids
The NEW ENGLAND JOURNAL of MEDICINE
FEBRUARY 25, 2021
Dexamethasone in Hospitalized Patients with Covid-19
The RECOVERY Collaborative Group*
Respiratory Support at Randomization
Dexamethasone
Usual Care
Rate Ratio (95% CI)
Invasive mechanical ventilation
Oxygen only
No oxygen received
All Patients
Chi-square trend across three categories: 11.4
0.50
0.75
1.00
1.50
2.00
Dexamethasone Better
Usual Care Better
Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.
RECOVERY trial: dexamethasone 6mg daily for up to 10 days (stopped at hospital discharge)
Survival benefit greatest among patients requiring mechanical ventilation (mortality 29% dexamethasone vs 41% standard of care [SOC], rate ratio 0.64 [0.51-0.81])
For patients requiring O2 but not mechanical ventilation, mortality 23% dexamethasone vs 26% SOC, rate ratio 0.82 [0.72-0.94]; no mortality benefit for patients not requiring O2
32

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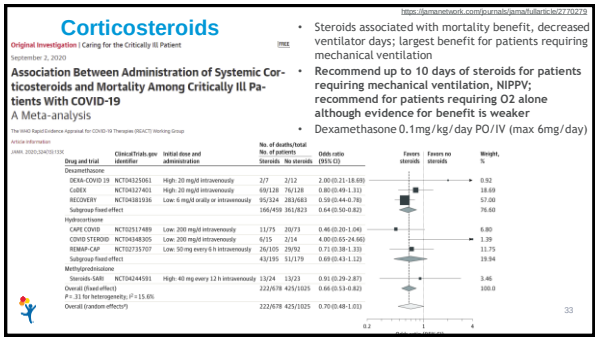
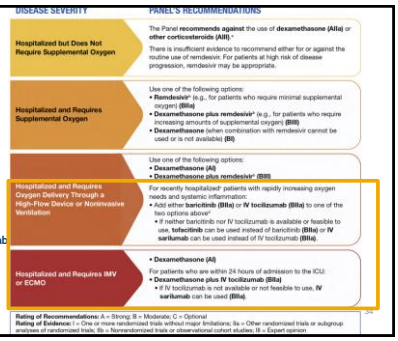

https://jamanetwork.com/journals/jama/fullarticle/2770279
Corticosteroids
Original Investigation | Caring for the Critically Ill Patient
FREE
September 2, 2020
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis
The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group
Drug and trial
ClinicalTrials.gov identifier
Initial dose and administration
No. of deaths/total No. of patients Steroids
No steroids
Odds ratio (95% CI)
Favors steroids
Favors no steroids
Weight, %
Dexamethasone
DEXA-COVID 19 NCT04325061 High: 20 mg/d intravenously 2/7 2/12 2.00 (0.21-18.69) 0.92
CoDEX NCT04327401 High: 20 mg/d intravenously 69/128 76/128 0.80 (0.49-1.31) 18.69
RECOVERY NCT04381936 Low: 6 mg/d orally or intravenously 95/324 283/683 0.59 (0.44-0.78) 57.00
Subgroup fixed effect 166/450 361/823 0.64 (0.50-0.82) 76.60
Hydrocortisone
CAPE COVID NCT02517489 Low: 200 mg/d intravenously 11/75 20/73 0.46 (0.20-1.04) 6.80
COVID STEROID NCT04348305 Low: 200 mg/d intravenously 6/15 2/14 4.00 (0.65-24.66) 1.39
REMAP-CAP NCT02735707 Low: 50 mg every 6 h intravenously 26/105 29/92 0.71 (0.38-1.33) 11.75
Subgroup fixed effect 43/195 51/179 0.69 (0.43-1.12) 19.94
Methylprednisolone
Steroids-SARI NCT04244591 High: 40 mg every 12 h intravenously 13/24 13/23 0.91 (0.29-2.87) 3.46
Overall (fixed effect) 222/678 425/1025 0.66 (0.53-0.82) 100.0
P = .31 for heterogeneity; I² = 15.6%
Overall (random-effects²) 222/678 425/1025 0.70 (0.48-1.01)
0.2
1
4
Steroids associated with mortality benefit, decreased ventilator days; largest benefit for patients requiring mechanical ventilation
Recommend up to 10 days of steroids for patients requiring mechanical ventilation, NIPPV; recommend for patients requiring O2 alone although evidence for benefit is weaker
Dexamethasone 0.1mg/kg/day PO/IV (max 6mg/day)
33

33

https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/

NIH Treatment Guidelines for COVID-19 in Hospitalized Adults

- Requiring O2: **remdesivir** +/- steroids
- High-flow/NIPPV: **steroids** +/- **remdesivir**
  - Recently hospitalized, escalating resp support, with systemic inflammation: add **baricitinib** or **tocilizumab**
- Intubated/ECMO: **steroids**
  - Recent ICU arrival, escalating support, systemic inflammation: add **tocilizumab**



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https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

Tocilizumab

Monoclonal antibody that blocks IL-6 receptor (so decreases activity of IL-6)

IL-6 is one of the predominant proinflammatory cytokines in patients with COVID19, has been associated with hyper-inflammation and severe disease

IL-6 drives CRP levels

Consider using high CRP to identify patients with hyper-inflammation in COVID-19

After tocilizumab, CRP may be less reliable lab marker for subsequent days / week

There may be increased risk of infection in patients receiving tocilizumab / tocilizumab with steroids

Sarilumab: IL-6 receptor antagonist, may use if tocilizumab not available; studies show similar benefit although with less data than for tocilizumab

35

35

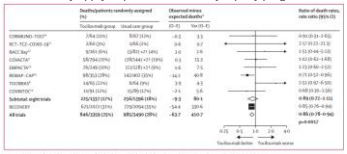
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00676-0/fulltext

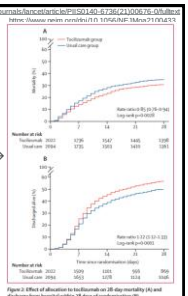
Tocilizumab

RECOVERY trial (UK): randomized to tocilizumab plus SOC vs SOC alone for patients with SpO2<92% and CRP>7.5mg/dL (75mg/L)

- Mortality benefit seen in tocilizumab group; SOC= some steroids
- Confirmed by REMAP-CAP (Canada) data, faster time to clinical improvement

Median time to tocilizumab 2 days for RECOVERY, <24h REMAP-CAP→ benefit may apply to patients with early rapidly progressive disease





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https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

Tocilizumab

Recommendation 7: Tocilizumab

Section last reviewed and updated on 2/17/2021

Last literature search conducted 2/11/2021

Recommendation 7: Among hospitalized adults with progressive severe* or critical COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (Conditional recommendation, Low certainty of evidence)**

- **Remarks:**
  - Patients, particularly those who respond to steroids alone, who put a high value on avoiding possible adverse events of tocilizumab and a low value on the uncertain mortality reduction, would reasonably decline tocilizumab.
  - In the largest trial on the treatment of tocilizumab, criterion for systemic inflammation was defined as CRP ≥75 mg/L.

Severity definitions:

*Severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen.

**Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock. In COVID-19, the most commonly reported form of end organ dysfunction is ARDS.

37

37

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

Baricitinib

Janus Kinase inhibitors: inhibit phosphorylation of proteins in the immune activation pathway that leads to inflammation in COVID19 (inhibits cellular response to IL-6)
JAK or JAK-STAT inhibitors

Remember, IL-6 is one of the predominant proinflammatory cytokines in patients with COVID19, has been associated with hyper-inflammation and severe disease

There may be increased risk of infection in patients receiving baricitinib / baricitinib with steroids
In non-COVID19 studies, longer courses of baricitinib associated with clotting risks

Tofacitinib: JAK inhibitor, minimal data in COVID19 but may consider if baricitinib not available

38

38

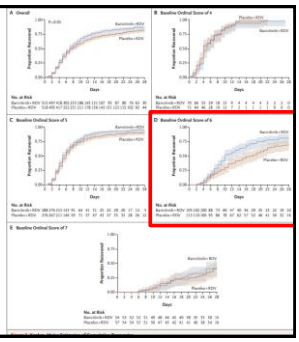
https://www.nejm.org/doi/10.1056/NEJMoa2031994

Baricitinib

ACTT-2 (NIH): randomized to baricitinib plus remdesivir vs remdesivir alone

- Improved time to recovery
- Most benefit for those receiving high-flow O2 or NIPPV, benefit not seen in those receiving mechanical ventilation/ECMO
- Study predated widespread steroid use

Should use either baricitinib or tocilizumab, not both together
No studies comparing baricitinib to tocilizumab



39

Back to those caveats…

These are all adult trials
Data for and experience with baricitinib in children is limited, tocilizumab somewhat limited

Consider consulting your infectious diseases or rheumatology colleagues for tocilizumab or baricitinib

Strength of evidence:

Strong: dexamethasone
Moderate/low: remdesivir, tocilizumab, baricitinib

40

40

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

What else: empiric antibiotics?

Antibacterials and antifungals

Last reviewed and updated 9/4/2020

Patients with COVID-19 often present to hospitals with viral pneumonia with accompanying febrile illness and respiratory symptoms. Differential diagnoses may include bacterial pneumonia, for which antibiotics are prescribed. Concerns for bacterial superinfections also exist. Studies performed early in the COVID-19 pandemic reported high percentages of antibiotic use in China (58-95%) [1, 217, 250], Spain (74%) [251], and New York (65%) [252]. These studies are not granular and do not report if they describe co-infection at presentation or the development of superinfection, limiting the ability to ascertain the reasons for antibiotic use.

Data reporting co-infection in patients presenting with COVID-19 for care is sparse. Rawson and colleagues reviewed 18 studies of human coronavirus infections reporting co-infections, of which nine were COVID-19 [253]. These cumulatively reported a bacterial and fungal co-infection rate of 8% (62/806). The studies evaluated were heterogeneous. One brief report of 393 patients in New York reported a bacteremia rate of 5.6%, which varied significantly between patients receiving invasive mechanical ventilation (15/126 [11.9%]) and those who were not (4/222 [1.8%]) [254]. Another study looked at 88,201 blood cultures performed during March 2020 in New York, comparing order volume, positivity, and etiologies between patients with COVID-19 and others during the time period [255]. The study found a significantly lower rate of bacteremia in COVID-19 patients (3.8%) than either COVID-19 negative (8%) or untested (7.1%) ($p<0.001$). When commensal skin organisms were excluded, the positivity rate in COVID-19 patients was 1.6% [255]. A study in Texas reviewed the use of antibiotics and incidence of coinfections in 147 PCR-positive COVID-19 patients [256]. Eighty-seven (59%) patients received empiric antibiotics, though none of the 47 (32%) patients with respiratory cultures had positive results. 112 patients (76%) had blood cultures collected also, and while nine were positive, eight of those were considered contaminants [256].

The apparent discordance between bacterial and fungal co-infection in patients with COVID-19 at presentation and the use of antibacterial therapy has potential negative effects, namely in antimicrobial resistance. Publications report on patients with severe

Rates of bacterial/fungal co-infection 5-8%

Large NYC study: 12% vs 2% bacterial co-infection for mechanical ventilation vs not

Bacterial co-infection w COVID19 higher in

- Critically ill hospitalized patients
- Those receiving immune-suppression

COVID19 chest imaging can look like anything: consolidation, streaky opacities, ground glass, uni- or bilateral, effusions

41

41

https://www.covid19treatmentguidelines.nih.gov/

What else: anticoagulation?

Antithrombotic Therapy in Patients with COVID-19

Last Updated: February 11, 2021

Summary Recommendations

Laboratory Testing

- In nonhospitalized patients with COVID-19, there are currently no data to support the measurement of coagulation markers (e.g., D-dimers, prothrombin time, platelet count, fibrinogen) **(AIII)**.
- In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured, although there is currently insufficient evidence to recommend either for or against using this data to guide management decisions.

Chronic Anticoagulant and Antiplatelet Therapy

- Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19 **(AIII)**.

Venous Thromboembolism Prophylaxis and Screening

- For nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIII)**.
- Hospitalized nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation **(AII)** (see the recommendations for pregnant individuals below). Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 **(AIII)**.
- There is currently insufficient evidence to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.
- Hospitalized patients with COVID-19 should not routinely be discharged from the hospital while on VTE prophylaxis **(AIII)**. Continuing anticoagulation with a Food and Drug Administration-approved regimen for extended VTE prophylaxis after hospital discharge can be considered for patients who are at low risk for bleeding and high risk for VTE, as per the protocols for patients without COVID-19 (see details on defining at-risk patients below) **(BII)**.
- There is currently insufficient evidence to recommend either for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the status of their coagulation markers.
- For hospitalized COVID-19 patients who experience rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion, the possibility of thromboembolic disease should be evaluated **(AIII)**.

Hospitalized Children With COVID-19

- For hospitalized children with COVID-19, indications for VTE prophylaxis should be the same as those for children without COVID-19 **(BIII)**.

42

42

https://www.covid19treatmentguidelines.nih.gov/

What else: anticoagulation?

- Meta-analysis: hospitalized patients with COVID19 found 14% prevalence of VTE
- Higher in studies actively screening for clots and among critically ill patients with COVID19
- ICU, Hematology, ID guidelines all recommend prophylactic anticoagulation for patients hospitalized with COVID19
  - Insufficient evidence to support empiric therapeutic anti-coagulation
- Minimal pediatric data: consider risk of clots for adolescents, patients with other risk factors, critically ill, and when respiratory status not improving

43

43

https://www.covid19treatmentguidelines.nih.gov/ https://pubmed.ncbi.nlm.nih.gov/33782242/

What else: prone positioning?

Review > Curr Opin Pediatr. 2021 Jun 1;33(3):319-324. doi: 10.1097/MOP.0000000000001009.

Prone positioning in children with respiratory failure because of coronavirus disease 2019

Matthew K Leroue [1], Aline B Maddux [2], Peter M Mourani [2]

Prone positioning improves oxygenation and outcomes in adults with moderate/severe ARDS receiving mechanical ventilation (pre-COVID19 studies)

For non-intubated adult patients:

> Overall, despite promising data, it is unclear which hypoxemic, nonintubated patients with COVID-19 pneumonia benefit from prone positioning, how long prone positioning should be continued, or whether the technique prevents the need for intubation or improves survival.[10]
>
> Appropriate candidates for awake prone positioning are those who can adjust their position independently and tolerate lying prone. Awake prone positioning is **contraindicated** in patients who are in respiratory distress and who require immediate intubation. Awake prone positioning is also **contraindicated** in patients who are hemodynamically unstable, patients who recently had abdominal surgery, and patients who have an unstable spine.[14] Awake prone positioning is acceptable and feasible for pregnant patients and can be performed in the left lateral decubitus position or the fully prone position.[15]

44

44

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

What doesn't work

Overview of IDSA COVID-19 Treatment Guidelines

Version 5.1 – August 27, 2021

		Setting and severity of illness			
		Ambulatory care: *mild-to-moderate disease*	***Hospitalized:*** *mild-to-moderate disease without need for suppl. oxygen*	***Hospitalized:*** *severe but non-critical disease (SpO₂ ≤94% on room air)*	***Hospitalized:*** *critical disease (e.g., in ICU needing MV, or septic shock, ECMO)*
1	*Hydroxychloroquine (HCQ)**	NA	Recommend against use ◐⊕⊕○	Recommend against use ◐⊕⊕○	Recommend against use ◐⊕⊕○
2	*HCQ* + azithromycin*	NA	Recommend against use ◐⊕⊕○○	Recommend against use ◐⊕⊕○○	Recommend against use ◐⊕⊕○○
3	*Lopinavir + ritonavir*	NA	Recommend against use ◐⊕⊕○	Recommend against use ◐⊕⊕○	Recommend against use ◐⊕⊕○
4-6	*Corticosteroids*	NA	Suggest against use ◐○○○	Suggest use ◐⊕⊕○ R: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used.**	Recommend use ◐⊕⊕○ R: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used.**
8-9	*Convalescent plasma*	Recommended only in the context of a clinical trial (knowledge gap)	Suggest against use ◐⊕⊕○○	Suggest against use ◐⊕⊕○○	Suggest against use ◐⊕⊕○○
13	*Tocilizumab*	NA	Suggest against use except in a clinical trial ◐○○○	Suggest against use except in a clinical trial ◐○○○	Suggest against use except in a clinical trial ◐○○○
16	*Bamlanivimab monotherapy*	NA	NA	Recommend against use ◐⊕⊕○	NA
19-20	*Ivermectin*	Suggest against use except in a clinical trial ◐○○○	Suggest against use except in a clinical trial ◐○○○	Suggest against use except in a clinical trial ◐○○○	Suggest against use except in a clinical trial ◐○○○

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https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofab318/6298585

What doesn't work

Recommendations 1 and 2: Hydroxychloroquine and Hydroxychloroquine + azithromycin

Section last reviewed and updated 12/23/2020

Last literature search conducted 12/14/2020

Recommendation 1. Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine*. (Strong recommendation, Moderate certainty of evidence)

- **Remark:** Chloroquine is considered to be class equivalent to hydroxychloroquine.

Recommendation 2. Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine* plus azithromycin. (Strong recommendation, Low certainty of evidence)

- **Remark:** Chloroquine is considered to be class equivalent to hydroxychloroquine.

Multiple large RCTs (including Solidarity and RECOVERY) failed to show benefit with HCQ
Several studies showed increased adverse events in patients receiving HCQ
- QT prolongation, associated arrhythmias
- Risk of QT prolongation/arrhythmia may be higher with HCQ+azithromycin

46

46

Flashback

https://www.nature.com/articles/s41591-021-01488-2, https://www.covid19treatmentguidelines.nih.gov/

Why trials matter: convalescent plasma

nature medicine — ARTICLES

OPEN

Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial

Philippe Bégin, Jeannie Callum, Erin Jamula, Richard Cook, Nancy M. Heddle

78% of planned enrollment after meeting stopping criteria for futility. In total, 940 patients were randomized, and 921 patients were included in the intention-to-treat analysis. Intubation or death occurred in 199/614 (32.4%) patients in the convalescent plasma arm and 86/307 (28.0%) patients in the standard of care arm—relative risk (RR) = 1.16 (95% confidence interval (CI) 0.94–1.43, P = 0.18). Patients in the convalescent plasma arm had more serious adverse events (33.4% versus 26.4%; RR = 1.27, 95% CI 1.02–1.57, P = 0.034). The antibody content significantly modulated the therapeutic effect of convalescent plasma. In multivariate analysis, each standardized log increase in neutralization or antibody-dependent cellular cytotoxicity independently reduced the potential harmful effect of plasma (odds ratio (OR) = 0.74, 95% CI 0.57–0.95 and OR = 0.66, 95% CI 0.50–0.87, respectively), whereas IgG against the full transmembrane spike protein increased it (OR = 1.53, 95% CI 1.14–2.05). Convalescent plasma did not reduce the risk of intubation or death at 30 d in hospitalized patients with COVID-19. Transfusion of convalescent plasma with unfavorable antibody profiles could be associated with worse clinical outcomes compared to standard care.

Before this study was published, two large RCTs of convalescent plasma for hospitalized patients stopped for futility (REMAP-CAP, CONCOR-1).

47

47

What doesn't work

JAMA | Original Investigation

Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19
A Randomized Clinical Trial

Eduardo López-Medina, MD, MSc; Pío López, MD; Isabel C. Hurtado, MD; Diana M Dávalos, MD, MPH, DrPH; Oscar Ramírez, MD, MPhil; Ernesto Martínez, MD; Jesus A. Olaya, MD; José M. Sosa, MD; Héctor Chavarriaga, MD, MS; Sócrates Herrera, MD; Beatriz Parra, PhD; Gerardo Libreros, PhD; Roberto Jaramillo, MD; Ana C. Avendaño, MD; Dilian F. Toro, MD; Miyerlandi Torres, DrPH; María C. Lesmes, MD; Carlos A. Ríos, MD; Isabella Calcedo, MD

Key Points

Question What is the effect of ivermectin on duration of symptoms in adults with mild COVID-19?

Findings In this randomized clinical trial that included 476 patients, the duration of symptoms was not significantly different for patients who received a 5-day course of ivermectin compared with placebo (median time to resolution of symptoms, 10 vs 12 days; hazard ratio for resolution of symptoms, 1.07).

Adverse effects of ivermectin include nausea, vomiting, diarrhea, headache, dizziness, tachycardia, hypotension, altered mental status, seizures

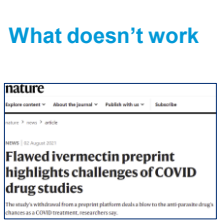
"but what about those other studies showing it works?"

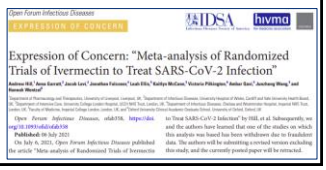
48

48

https://retractionwatch.com/2021/08/10/ivermectin-meta-analysis-to-be-retracted-revised-say-authors/
https://www.nature.com/articles/d41586-021-02081-w
https://academic.oup.com/ofid/article/8/8/ofab394/6346765

What doesn't work





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https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofab318/6298585

What doesn't work

From an editorial accompanying an August 2021 meta-analysis of ivermectin for COVID19. Note that the meta-analysis manuscript is currently being revised after retraction of one of the largest positive studies included in their analysis.

"Very early enthusiasm for the use of ivermectin for COVID-19, derived from in vitro data, was tempered by subsequent pharmacokinetic data suggesting effective doses to achieve IC50 against the virus were not readily achievable in humans."

"…we are left with a compelling meta-analysis….suggesting a modest to large benefit of a low-cost, widely available, well-tolerated therapy for COVID-19…but based on studies with small sample sizes, design flaws, incomplete results, or some combination thereof"

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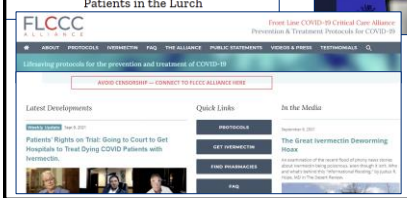
https://www.nbcnews.com/tech/tech-news/ivermectin-demand-drives-trump-telemedicine-website-rcna1791
https://time.com/6092368/americas-frontline-doctors-covid-19-misinformation/?utm_source=twitter&utm_medium=social&utm_campaign=editorial&utm_term=politics_covid-19&linkId=129188380

What doesn't work



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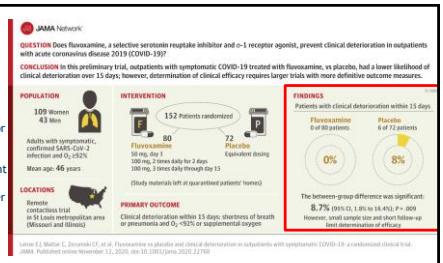
What's next?

- Fluvoxamine
  - Oral SSRI
  - Being studied for use in non-hospitalized adults to prevent clinical progression after COVID19 infection
- Molnupiravir
  - Oral antiviral
  - Nucleoside analog that binds to SARSCOV2 viral RNA-dependent RNA polymerase and inhibits viral replication by introducing mutations
  - Being studied for use in non-hospitalized adults with risk factors for severe COVID19



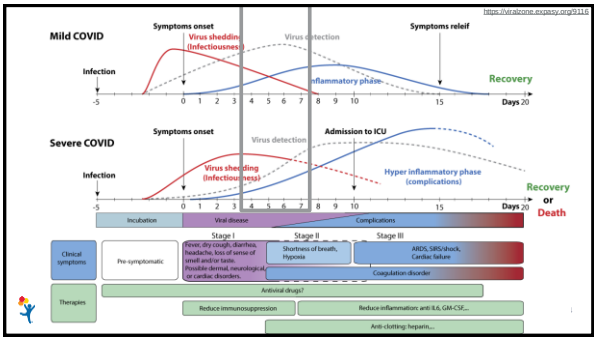
52

Clinical scenario 1:

15 year old with obesity and obstructive sleep apnea has had headache and sore throat for 4 days and today was having trouble catching their breath after going up the stairs. In the ED, their SpO2 is 87% and improves with 4L O2 by nasal cannula. Nasopharyngeal swab is positive for COVID19.

Which (if any) pharmacologic treatments for COVID19 would you choose?

53



54

https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/

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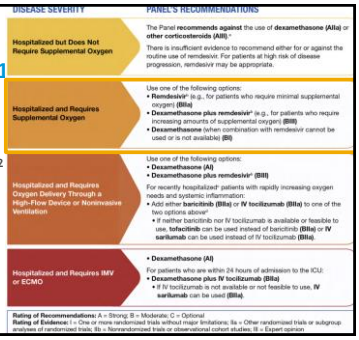

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Clinical scenario 1 continued:

Your patient starts receiving remdesivir and dexamethasone. Labs notable for WBC 2.5 (ALC 500) and CRP 14mg/dL. Overnight, they are requiring increased respiratory support. After trying a face mask instead of nasal cannula and then trying high flow, they are still dyspneic and struggling to maintain SpO2 of 91%. You are concerned they may need positive pressure support and plan to call the ICU.

Which (if any) pharmacologic treatments for COVID19 would you add?

56

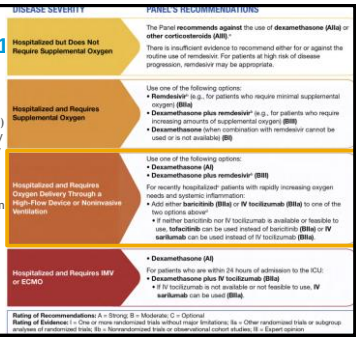
56

https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/

Clinical scenario 1 continued:

Your patient starts receiving **remdesivir and dexamethasone**. Labs notable for WBC 2.5 (ALC 500) and **CRP 14mg/dL**. Overnight, they are requiring increased respiratory support. After trying a face mask instead of nasal cannula and then trying high flow, they are still dyspneic and struggling to maintain SpO2 of 91%. You are **concerned they may need positive pressure support** and plan to call the ICU.

Which (if any) pharmacologic treatments for COVID19 would you add?



57

Clinical scenario 2:

13 year old who had a heart transplant 2 years ago and has chronic renal insufficiency was exposed to someone with COVID19 recently and now has had cough and fatigue for 3 days. SpO2 is 96% with no respiratory distress. Nasal swab is positive for COVID19. They received two doses of Pfizer COVID19 vaccine several months ago.

Which (if any) pharmacologic treatments for COVID19 would you recommend?

58

https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/

Clinical scenario 2:

13 year old who had a **heart transplant** 2 years ago and has **chronic renal insufficiency** was exposed to someone with COVID19 recently and now has had cough and fatigue for 3 days. **SpO2 is 96% with no respiratory distress.** Nasal swab is positive for COVID19. They received two doses of Pfizer COVID19 vaccine several months ago.

Which (if any) pharmacologic treatments for COVID19 would you recommend?

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider in ED or an In-Person or Telehealth Visit	Anti-SARS-CoV-2 monoclonal antibody products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progression, as defined by the EUA criteria (treatments are listed in alphabetical order):[a] • **Casirivimab plus imdevimab**; or • **Sotrovimab** At this time, the Panel **recommends against** the use of **bamlanivimab plus etesevimab** in these patients due to an increase in the proportion of potentially resistant variants **(AIII)**.[b] See text for details. The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[c]
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen*	There is insufficient evidence to recommend either for or against the continued use of remdesivir, dexamethasone, and/or baricitinib. Review the text below when considering the use of any of these agents after hospital discharge.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured*[d]	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use should not exceed 10 days) with careful monitoring for adverse events **(BIII)**. There is insufficient evidence to recommend either for or against the use of remdesivir. When considering the use of remdesivir, review the text below for further discussion. The Panel **recommends against** the use of **baricitinib** in this setting, except in a clinical trial **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

59

Questions & Discussion

Flames from the LNU Lightning Complex fires burn in unincorporated Napa County, Calif., on Tuesday.

https://www.npr.org/2020/08/21/904552759/wildfires-rage-on-in-california-as-fire-crews-and-evacuees-grapple-with-covid-ri

60