LITERATURE REVIEW SARS CoV-2 Treatment

September 13th, 2021

SUPPORTIVE CARE

VENTILATION

- Though mostly anecdotal, there is some evidence on the ventilator settings and differing characteristics of COVID-19 associated ARDS. Ventilator setting recommendations include:
    - Low TV, ≤ 4-8 mL/kg ideal body weight
    - Plateau pressures <30 cm H_2O
    - PEEP >10 cm H2O
    - Oxygen administration at an SpO2 < 90% - 96%.
    - Starting RR of 16 breaths/min.
    - Early prone positioning
        - If prone positioning fails, use recruitment maneuvers and high PEEP strategies, pulmonary vasodilators, neuromuscular blocking agents, and/or ECMO.
- The most experienced team member should perform intubation with as few assistants as possible to reduce exposure. Bag-mask ventilation generates aerosols and should be minimized by performing prolonged pre-oxygenation. Rapid sequence induction with muscle relaxants will reduce coughing.
- In patients who develop hypercapnia, increase VT to ~7.7.
- For timing of intubation:
    - If a patient is on nasal high-flow oxygen therapy, the ROX index [SpO2/(FiO2 x RR)] can be used. If after 12 hours, patients have a ROX index of <3.85, initiate intubation.
    - For NCP patients, if PaO2/FiO2 is <150 mmHg (1mmHg = 0.133 kPa), initiate intubation if receiving more than 2 hours of nasal high-flow therapy or non-invasive ventilation.
- Two recent studies found that self-proning improved oxygenation parameters in adults with COVID-19 with noninvasive ventilation
    - Some patients may be unable to tolerate this or sustain higher oxygenation parameters upon returning to the supine position
- Among the noninvasive modalities recent data suggests HFNC is superior to NIV. The preference for HFNC is based upon limited and inconsistent data, which, on balance, favors HFNC compared with NIV in patients with non-COVID-19-related acute hypoxemic respiratory failure.

ECMO

- ECMO should be considered if mortality rate approaches 50%, initiate if 80%.
- ECMO should be considered if one following criteria are met:
    - (1) PaO2/FiO2<100mmHg
    - (2) P(A-a) O2>600mmHg
    - (3) pH<7.2 and plateau pressure >30 cmH2O with respiratory rate > 35 breaths per minute
    - (4) <65 years old
    - (5) NO contraindications
    - (6) Severe air leak syndrome
    - (7) Complicated by cardiogenic shock or cardiac arrest
- Contraindications include: multi-organ failure, contraindication to anticoagulation, high mechanical vent for more than 7 days, obesity

ANTICOAGULATION

- D-dimer and FDP levels may progressively increase with COVID-19 exacerbation, resulting in acro-ischemia
- Prophylactic anticoagulation with LMWH (preferred) or UFH (CrCl <15ml/min or RRT) is recommended for all inpatient adults with COVID-19
- Therapeutic anticoagulation with rivaroxaban and other DOACs did not improve clinical outcomes and increased bleeding risk [ACTION trial]

- Fondaparinux may be used for HIT
- Antiplatelet agent Dipyridamole has been found to suppress SARS-CoV-2 replication in vitro. A proof of concept trial involving 31 patients with COVID-19 found that dipyridamole supplementation was associated with decreased D-Dimer concentration, improved platelet and lymphocyte counts, and improved clinical outcomes compared to control patients.

OUTPATIENT MANAGEMENT OF COVID-19

First Steps

- Advise for methods to reduce COVID-19 transmission
- Advise patients on when to seek health care provider and treatment
- Triage patients with COVID-19 symptoms via tele-health visits prior to receiving in-person care
- Purchasing a pulse oximeter is not recommended, but if the patient already owns an oximeter, advise on proper usage and consider the oximetry data with overall clinical picture

Dyspnea

- Home observation*: no dyspnea, no dyspnea + risk factors for severe disease; mild dyspnea without risk factors for severe disease
- Clinic evaluation*: mild dyspnea + O2 sat 91-94%; mild dyspnea + risk factors for severe disease; moderate dyspnea in any patient
- ED evaluation: severe dyspnea, O2 sat ≤90%, concerning altered mental status, other signs of hypoxia

*Telehealth follow-up mostly scheduled on days 4, 7, 10. If high concern for exacerbation, follow-up within 24 hours.

Therapy for Mild to Moderate COVID-19

Timing: Administer within 10 days of symptom onset

- **Casirivmmab-Imdevimab (600-600 mg) (REGEN-COV)**
- **Sotrovimab (500 mg)***

Supportive care: hydration, acetaminophen (fever, myalgia), OTC cough meds (cough disturbing sleep), ambulation/activity as tolerated

*Sotrovimab approved per EUA but not fully recommended due to clinical trial results currently unavailable

Note: *Bamlanivimab-Etesevimab (700-1400 mg) distribution suspended on 06/25/21 due to likely resistance in variants*

Therapies NOT Approved for Outpatient Management of COVID-19

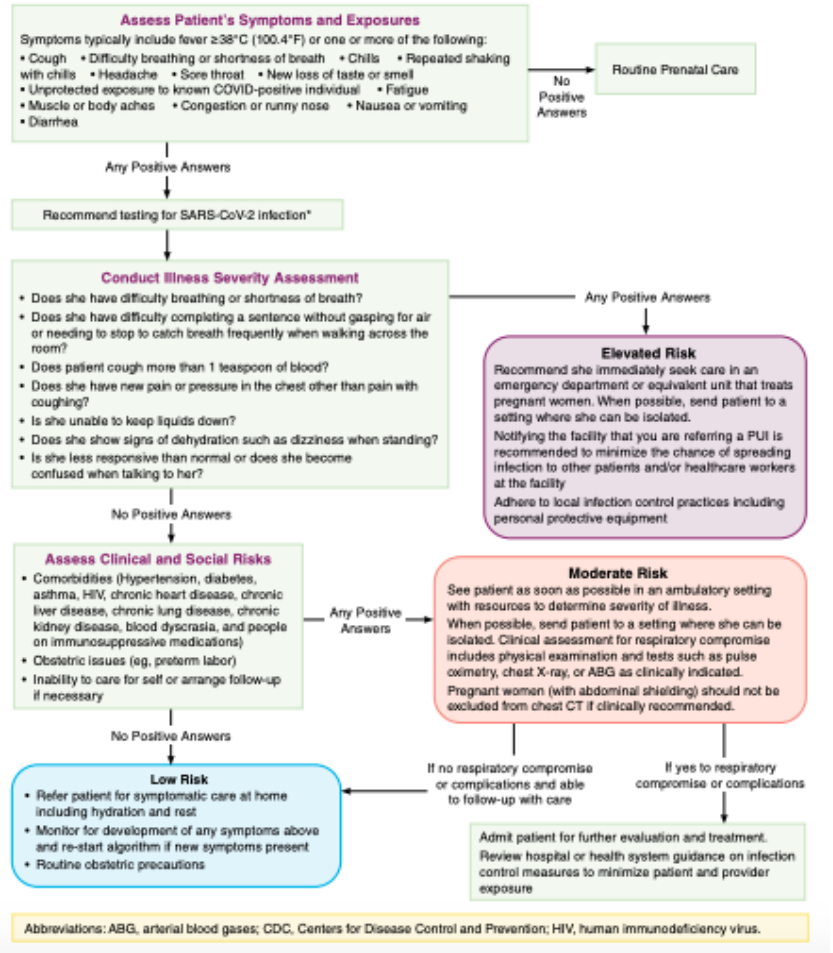
- Bamlanivimab 700 mg + Etesevimab 1,400 mg [resistance]
- High-titer convalescent plasma [remains investigational for outpatient use]
- Chloroquine/Hydroxychloroquine +/- Azithromycin, Lopinovir/ Ritoniavir
- Systemic glucocorticoids in the absence of other indications [no efficacy]

- Antimicrobial therapy (e.g. azithromycin, doxycycline, ivermectin) in the absence of other indications [insufficient evidence]
- Fluvoxamine [insufficient evidence]
- Anticoagulants and antiplatelet therapy should not be initiated for prophylaxis in outpatient setting unless patient has other indications for therapy

COVID-19 MANAGEMENT IN SPECIAL POPULATIONS

PREGNANCY

- The American College of Obstetricians and Gynecologists (ACOG) has developed an algorithm in the outpatient management of COVID-19 in pregnant women



- ACOG recommends that pregnant individuals have access to COVID-19 vaccines.
- COVID-19 vaccines should be offered to lactating individuals similar to non-lactating individuals.
- A study that used data from three vaccine safety reporting systems in the United States reported that the frequency of adverse events among 35,691 vaccine recipients who identified as pregnant was similar to the frequency observed among nonpregnant patients.

- Local injection site pain, nausea, and vomiting were reported slightly more frequently in pregnant people than in nonpregnant people.
- Other systemic reactions were reported more frequently among nonpregnant vaccine recipients, but the overall reactogenicity profile was similar for pregnant and nonpregnant patients.

CHILDREN

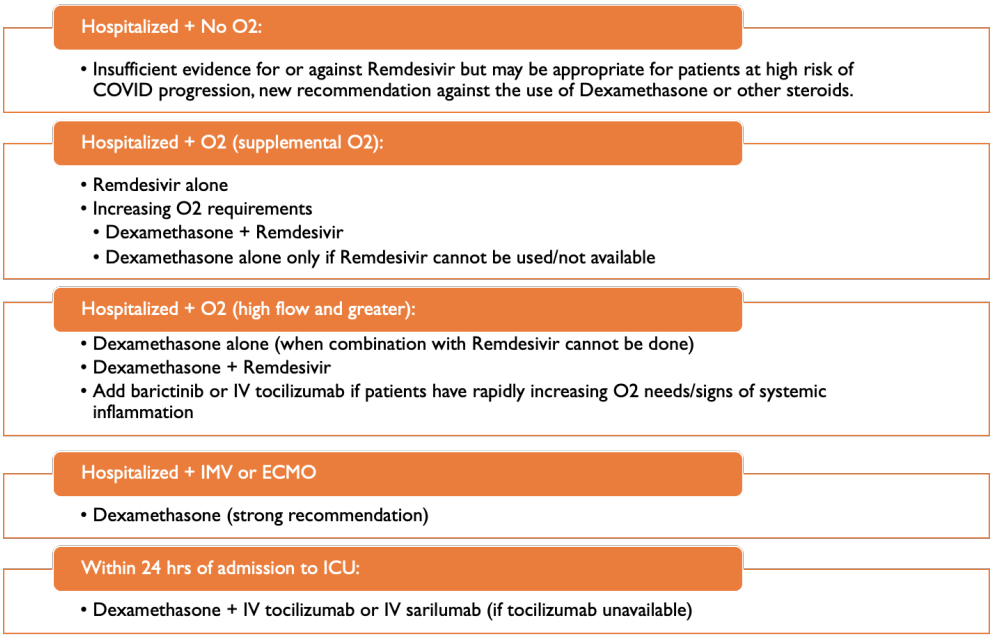
- Most children with mild or moderate COVID-19, even with risk factors, will recover without specific therapy
- Casirivimab plus imdevimab may be considered on a case-by-case basis for nonhospitalized children who meet the EUA criteria, especially those who meet more than one criterion or are aged ≥16 years
- Remdesivir is recommended for
    - Hospitalized children aged ≥12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen
    - Hospitalized children aged ≥16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen regardless of whether they have risks factors for severe disease
- Dexamethasone for hospitalized children with COVID-19 is recommended for those who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation
- Convalescent plasma is recommended against for hospitalized children with COVID-19 who do not require mechanical ventilation, except in clinical trial
- Sarilumab is recommended against for hospitalized children with COVID-19 or MIS-C, except in clinical trial
- IVIG and/or corticosteroids are the first-line therapies for children with MIS-C
    - Interleukin-1 antagonist has been used for refractory cases
- After an explicit, evidence-based review of all available data, the Advisory Committee on Immunization Practices (ACIP) has issued interim recommendations for use of the Pfizer-BioNTech COVID-19 vaccine in persons aged ≥12 years for the prevention of COVID-19, the use of the Moderna-1273 COVID-19 vaccine in persons aged ≥ 18 years, and the use of the Janssen (Johnson & Johnson) COVID-19 vaccine in persons aged ≥ 18 years.

COVID-19 MANAGEMENT IN THE HOSPITAL SETTING

- **At hospital discharge: recommendation AGAINST continuing Remdesivir, Dexamethasone, or Baricitinib**
- **Hospitalized + No O2:** insufficient evidence for or against remdesivir but may be appropriate for patients at high risk of COVID progression, new recommendation against the use of Dexamethasone or other steroids.
- **Hospitalized + O2** (supplemental O2):
    - Remdesivir alone
    - Increasing O2 requirements - Dexamethasone + Remdesivir
    - Dexamethasone alone only if Remdesivir cannot be used/not availible
- **Hospitalized + O2 (high flow and greater)**:
    - Dexamethasone alone (when combination with remdesivir cannot be done)
    - Dexamethasone + Remdesivir
    - Add baricitinib or IV tocilizumab if patients have rapidly increasing O2 needs/signs of systemic inflammation

- **Hospitalized + IMV or ECMO**
  - Dexamethasone (strong recommendation)
  - Within 24 hrs of admission to ICU: Dexamethasone + IV tocilizumab or IV sarilumab (if tocilizumab unavailable)

OR ALTERNATIVELY THIS GRAPHIC:



MEDICAL THERAPIES

(could add graphic that summarizes the doses for recommended medical therapies-made 2 versions)

REMDESIVIR:

- Nucleotide prodrug of an adenosine analog, binds viral RNA-dependent RNA polymerase inhibiting viral replication
- Loading dose of 200 mg IV on day 1, 100 mg daily for 4d or until hospital discharge (up to 10 days if no clinical improvement, on ventilator, on ECMO)
- not recommended for patients with eGFR < 30

DEXAMETHASONE

- 6 mg IV or PO once daily for up to 10 days or until hospital discharge

BARICITINIB:

- Jak-1 & Jak-2 inhibitor
- Dosing dependent on eGFR, given for up to 14 days or until hospital discharge
- EGFR > 60: Baricitinib 4 mg PO qd
- EGFR 30-<60 Baricitinib 2 mg PO qd
- EGFR 15-<30 Baricitinib 1 mg PO qd

TOFACITINIB: Jak-1, Jak-3 inhibitor, partial Jak-2 inhibitor

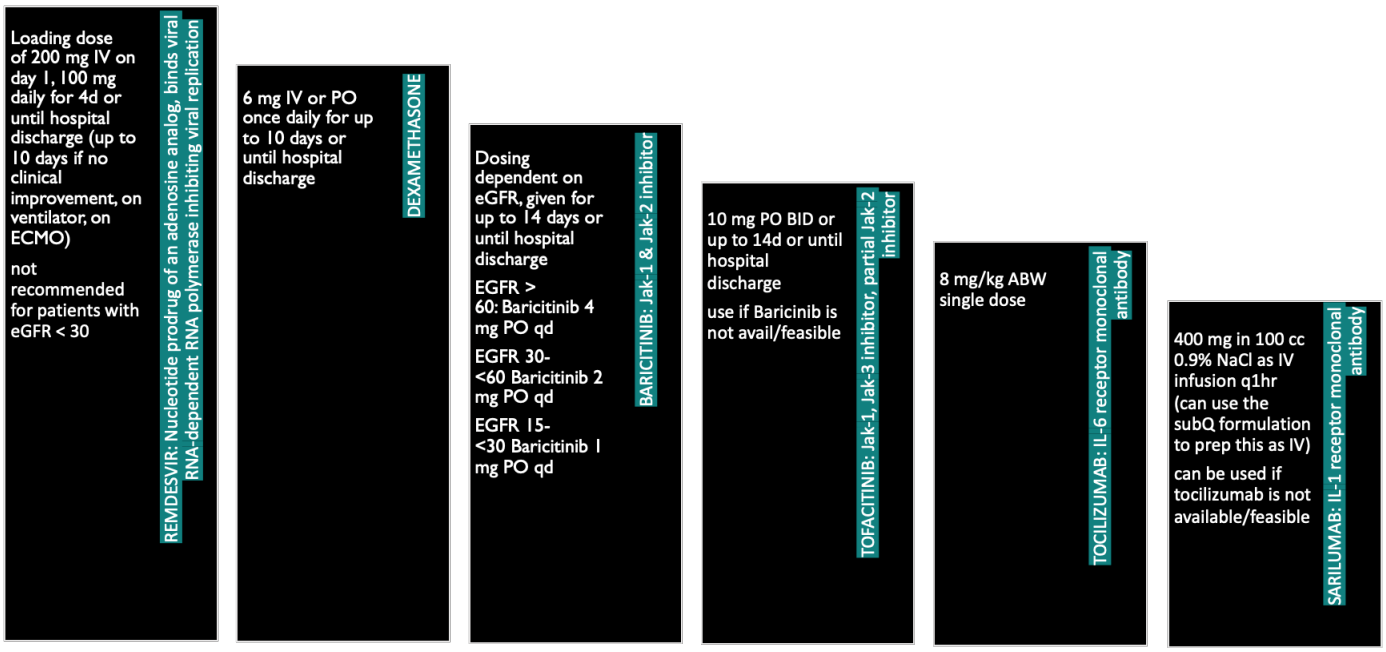
- 10 mg PO BID or up to 14d or until hospital discharge
- use if Baricinib is not avail/feasible

TOCILIZUMAB:

- IL-6 receptor monoclonal antibody
- 8 mg/kg ABW single dose

SARILUMAB:

- IL-1 receptor monoclonal antibody
- 400 mg in 100 cc 0.9% NaCl as IV infusion q1hr (can use the subQ formulation to prep this as IV)
- can be used if tocilizumab is not available/feasible



DIRECT ACTING ANTIVIRALS

REMDESIVIR

- Remdesivir is the only FDA-approved COVID-19 treatment as of 08/30/21
    - Approved for: age > 12 years old, weight > 40 kg
- Final report of ACTT-1 trial:
    - (n=1063, double blinded, placebo-controlled, RCT on Remdesivir efficacy)
    - Shorter time to recovery compared to placebo (median 10 days vs 15 days), shorter length of hospital stay (median 12 vs 17 days), reduced mortality through day 14 (HR 0.55 [95% CI: 0.36-0.83], greater efficacy when administered early
- Adverse effects:
    - Elevated hepatic transaminases, nausea, diarrhea, rash, renal impairment, hypotension. Adverse events occurred more commonly in ventilated patients

IVERMECTIN

- According to the COVID-19 Treatment Panel, there is insufficient evidence and more clinical trials are needed to understand the role of ivermectin in the treatment of COVID-19
- Ivermectin has been shown to inhibit replication of the SARS-CoV-2 virus

NONSPECIFIC ANTI-INFLAMMATORY

DEXAMETHASONE

- The RECOVERY trial (n=2104) has shown that dexamethasone reduces mortality in ventilated patients by one-third and in patients solely on oxygen by one-fifth.
    - 6 mg PO or IV QD dexamethasone was given to all patients (n=2104) for 10 days and compared to a randomized control group (n=4321) receiving usual care. The compared treatment arms were Lopinavir-Ritonavir, Hydroxychloroquine (discontinued), Azithromycin, Tocilizumab, and Convalescent plasma.
- Dexamethasone has not shown reduction in mortality of patients not using respiratory support
- According to the NIH recommendations released on April 21, 2021, dexamethasone is not recommended for outpatient management of COVID-19
- Low-dose dexamethasone for ICU patients with COVID-19 who require oxygen supplementation or mechanical ventilation is recommended based on accumulating evidence that glucocorticoids reduce mortality in such patients.
- Adverse Effects:
    - The primary short-term adverse effect hypoglycemia
    - With prolonged use: glaucoma, cataracts, fluid retention, hypertension, psychological effects, weight gain, or increased risk of infections and osteoporosis
- Dexamethasone has shown to be a moderate inducer of CYP3A4 and thus its use must be monitored for drug interactions

METHYLPREDNISONE

- A Brazilian study evaluated the use of short-term methylprednisone as adjunct therapy for hospitalized patients, over the course of 28-days. (Prado Jeronimo, C.M. et al, 2020)
- Methyprednisone was given to one group (n=194), dosed for 5 days with twice-daily 0.5 mg/kg IV, and then compared to a randomized control group (n=199). Mortality was not different at day 28 between the two groups; however, mortality among patients over the age of 60 decreased in the MP group.
- As a caution, insulin should be monitored in patients receiving MP.

COLCHICINE

- A press release from the Montreal Heart Institute announced on Jan. 22, 2021 the preliminary results of a clinical trial using Colchicine to treat COVID-19. The results showed that Colchicine reduced the risk of death or hospitalizations by 21% compared to placebo. The colchicine was effective at preventing the cytokine storm.
    - The trial (n=4488) included people who had tested positive via naso-pharyngeal PCR, and randomly assigned them to colchicine or placebo cohorts. The colchicine was shown to reduce hospitalizations by 25%, the need for ventilation by 50%, and deaths by 44%.
    - This would be a good candidate for an oral treatment for non-hospitalized patients.
- On April 21, 2021, the NIH panel recommends against the use of colchicine in hospitalized patients, except for clinical trial purposes. There is insufficient evidence to recommend either for or against use of colchicine in non-hospitalized COVID-19 patients.
- As of July 8th, 2021 the Panel officially recommends against the use of colchicine for the treatment of hospitalized patients with COVID-19.

FLUVOXAMINE

- An SSRI approved by FDA for treatment of Obsessive-Compulsive Disorder (OCD) and used for depression therapy
- Research has shown the anti-inflammatory effect of fluvoxamine in its ability to bind to the sigma-1 receptor in immune cells, resulting in decreased inflammatory cytokine production
- There is insufficient evidence to recommend either for or against use of fluvoxamine in COVID-19 treatment

BUDESONE

- Based on available clinical trial data, the Panel has determined that there is currently insufficient evidence to recommend either for or against the use of inhaled budesonide for the treatment of COVID-19.

MONOCLONAL ANTIBODIES

BAMLANIVIMAB + ETESEVIMAB

- On February 23, 2021, Emergency Use Authorization was given for the use of Bamlanivimab 700 mg and Etesevimab 1,400 mg combo for outpatient treatment of patients with mild to moderate COVID-19 infection who are at high risk of progressing to severe disease and/or hospitalization
    - They recommend against the use of this combination treatment in hospitalized COVID-19 patients, with exceptions for those in clinical trial
- On March 2021, the panel recommended AGAINST the use of monotherapy with Bamlanivimab monotherapy
- Bamlanivimab and etesevimab are not authorized for use in patients:
    - who are hospitalized due to COVID-19, OR
    - who require oxygen therapy due to COVID-19, OR
    - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation
- On April 16, 2021 the U.S. Food and Drug Administration revoked the emergency use authorization (EUA) that allowed for the investigational monoclonal antibody therapy bamlanivimab, *when administered alone*, to be used for the treatment of mild-to-moderate COVID-19 in adults and certain pediatric patients.
- On June 25, 2021 the FDA paused distribution of bamlanivimab and etesevimab until further notice.

- On August 31, 2021 the FDA provided EUA bamlanivimab and etesevimab, administered together, only in states, territories, and U.S. jurisdictions in which recent data shows the combined frequency of variants resistant to bamlanivimab and etesevimab administered together is less than or equal to 5%

TOCILIZUMAB

- A study reviewing clinical trials in China and by the FDA suggest that Tocilizumab may be indicated in patients with cytokine release syndrome (CRS) and diffuse lung injury. The clinical trial found reduction in lung lesions, improvements in oxygen level and respiratory function, and reduction in fever to normal temperature.
    - Study limitations: small sample size (n = 14), all patients treated with methylprednisolone concomitantly
- A multicenter study (n = 63) in showed significant improvement in COVID patients with a pro-thrombotic, pro-inflammatory profile (classified as having 3 of the following: Ferritin >1000 ng/mL, CRP, D-Dimer 10x normal, LDH 2x normal). Administration of TCZ within 6 days of admission was associated with a higher chance of survival. (Sciascia et al. 05/26/2020)
    - TCZ was administered either IV (8 mg/kg) or SC (324 mg), with a 2nd dose in 52 out of 63 patients.
- Another retrospective study by the University of Maryland confirmed similar improvements in COVID patients with CRS due to Tocilizumab treatment combined with lopinavir, methylprednisolone, and oxygen therapy.
    - Both studies reviewed 1-hour infusion of tocilizumab up to 800 mg (max dosage) with some adverse effects including gastrointestinal perforations in patients with diverticulitis and concomitant high dosage corticosteroid use.
- Tocilizumab should not be used in pregnant patients and has not been found to be hepatotoxic or nephrotoxic thus far.
- On February 2021, a New England Journal of Medicine paper revealed that the use of tocilizumab did not result in significantly better clinical status or lower mortality.
- On March 5, 2021, the COVID-19 Treatment Panel updated its recommendations on the use of tocilizumab:
    - They recommend the use of tocilizumab + dexamethasone in certain hospitalized COVID patients who are in rapid respiratory decompensation. These patients include:
        - ICU patients admitted within 24 hours and require respiratory support
        - Recently hospitalized patients (not ICU) with increasing oxygen requirements and have significantly increased markers of inflammation
- On May 27, 2021, the COVID-19 Treatment Panel recommended the use of tocilizumab in combination with dexamethasone alone or dexamethasone plus remdesivir for the treatment of COVID-19 in hospitalized patients on high-flow oxygen or noninvasive ventilation who have evidence of clinical progression or increased markers of inflammation
- On June 24, 2021 the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the drug Actemra (tocilizumab) for the treatment of hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

SARILUMAB

- REMAP-CAP trial recently updated results showed similar efficacy for sarilumab and tocizumab when compared to placebo plus dexamethasone
    - Patients who received sarilumab and dexamethasone demonstrated reduced mortality and shorter time to ICU discharge.
- Currently recommended to use sarilumab when tocilizumab is not availible/feasible.

REGEN-COV ANTIBODY COCKTAIL

- The REACH Trial (COVPN 3502/REGN 2069) is testing the ability to prevent the acquisition of SARS-COV-2 through the combination treatment of casirivimab and imdevimab antibody cocktail.

- This cocktail is designed to bind the SARS-COV-2 virus and prevent the virus from entering into healthy cells
- Study enrollment consists of ~3,500 adults and adolescents who share a household with a person who recently tested positive for COVID-19
- Preliminary results from Regeneron show decreased viral loads and decreased disease burden, measured by fewer weeks of viral shedding, fewer weeks of high viral load shedding, and fewer total symptomatic weeks.
- The authorized dosage has been reduced from a single intravenous (IV) infusion of casirivimab 1,200 mg plus imdevimab 1,200 mg to casirivimab 600 mg plus imdevimab 600 mg.
- The same doses of casirivimab and imdevimab may now be administered by subcutaneous (SQ) injection when IV infusion is not feasible or may delay treatment.
- As of July 30, 2021 the authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab administered together as a single intravenous infusion or by subcutaneous injection as soon as possible after positive SARS-CoV-2 viral testing and within 10 days of symptom onset

SOTROVIMAB

- On May 26, 2021, the FDA issued an EUA for the anti-SARS-CoV-2 monoclonal antibody sotrovimab for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe COVID-19.

KINASE INHIBITORS

TOFACITINIB

- The STOP-COVID trial demonstrated that use of of tofacitinib was associated with a decreased risk of respiratory failure and death (risk ratio 0.63).
    - All-cause mortality within 28 days occurred among 2.8% of the participants in the tofacitinib arm (n = 144) and 5.5% in the placebo arm (n = 145)
    - Approximately 80% of participants in each arm also received corticosteroids.
    - Serious adverse events occurred in 14.2% of the participants in the tofacitinib group and in 12.0% in the placebo group.[26]
- Tofacitinib recommended as an alternative to baricitinib only when baricitinib is not available or not feasible to use (BIIa) with the rationale that they have overlapping mechanisms of action.

BARICITINIB

- Baricitinib has received EUA approval for treatment of COVID-19 in patients 2 years of age or older as of 11/23/2020
    - The ACTT-2 trial was published on Dec. 11,2020, which showed that Baricitinib in combination with Remdesvir was more effective in reducing recovery time and accelerating recovery time than Remdesvir alone. The trial group (n=1033) compared using a 4-mg dose of Baricitinib in combination with Remdesivir, versus Remdesivir alone. Investigators found a 1-day reduction in median time overall in recovery. They defined recovery as either coming off supplemental oxygen or being discharged.
- Patients receiving combination therapy on high-flow oxygen or non-invasive ventilation at enrollment recovered faster (within 10 days versus 18 for control) and there were fewer serious adverse events and infections in the combo cohort. The 28-day mortality was 5.1% in the combination cohort and 7.8 in the control.Baricitinib received EUA for a 4-mg dose for COVID patients.
- In circumstances when corticosteroids cannot be used, the Panel recommends the use of baricitinib in combination with remdesivir for COVID-19 hospitalized, non-intubated patients who require oxygen supplementation.
- On May 27, 2021, the COVID-19 Treatment Panel recommended the use of baricitinib in combination with dexamethasone alone or dexamethasone plus remdesivir for the treatment of COVID-19 in hospitalized patients

on high-flow oxygen or noninvasive ventilation who have evidence of clinical progression or increased markers of inflammation
- As of July 8th, 2021 the Panel recommends against the use of baricitinib in combination with tocilizumab.

ADVANCED THERAPY MEDICINAL PRODUCTS (ATMP)

CONVALSECENT PLASMA

- Convalescent plasma is FDA approved for use in clinical trials, patients with severe or immediately life-threatening laboratory confirmed COVID-19, and single patient emergency IND approval (FDA 5/1/2020)
- A study performed at Houston Methodist hospitals (n = 25) found that 36% of patients improved from baseline after 7 days and 76% improved after 14 days after 300 mL convalescent plasma obtained from 9 healthy donors who had recovered from COVID-19 was transfused (Salazar et al 5/27/2020)
    - Study limitations: n = 25, no control group, all patients were treated with HQ + azithromycin, 2 patients were treated with remdesvir, some with ribavarin, and some with tocilizumab and methylprednisone
    - overall decrease in CRP and no increase in LFTs; 20 out of 25 patients were discharged, all but 2 patients on ventilation and ECMO were weaned off
    - Further study is needed to assess efficacy of convalescent plasma as a stand-alone treatment
- Another randomized clinical trial from 7 medical centers in Wuhan, China compared a standard treatment group (n = 51) to a standard treatment plus convalescent plasma group (n=52)
    - 98.3% of patients in the experimental group with severe disease recovered within 28 days compared to the control group (68.2%)
    - There was no statistical difference for recovery within 28 days between the control and experimental group for patients with life-threatening disease
    - No statistically significant decrease in time to clinical improvement between the experimental and control groups

OTILIMAB AND LENZILUMAB

- As of July 8th, 2021 the Panel has determined that there is insufficient evidence to recommend either for or against the use of GM-CSF inhibitors for the treatment of hospitalized patients with COVID-19.

ANTIPARASITICS

NITAZOXANIDE

- The Panel recommends against the use of nitazoxanide for the treatment of COVID-19, except in a clinical trial.

AGENTS NO LONGER RECOMMENDED FOR USE

- **HYDROXYCHLOROQUINE/AZITHROMYCIN/CHLOROQUINE**
    - The FDA revoked EUA for COVID-19; cannot be used outside an authorized clinical trial.

- There is no clear evidence for the benefit of hydroxychloroquine in the treatment of patients hospitalized with COVID-19.
- As of July 8th, 2021 the Panel officially recommends against the use of chloroquine or hydroxychloroquine and/or azithromycin for the treatment of COVID-19 in hospitalized patients and in non-hospitalized patients.

- **TENOFOVIR**
- **BAMLANIVIMAB MONOTHERAPY**

VACCINES

AUTHORIZED AND RECOMMENDED COVID-19 VACCINES

Vaccine*	Number of Doses	FDA Status	Efficacy	Age	Side Effects	Allergies
Pfizer Vaccine	2 shots 21days apart+	In use	95%	12+	Pain, swelling, redness at injection site, chills, tiredness, headaches, fever, chills, symptomatic acute myocarditis in adolescents, multisystem inflammatory syndrome in children, anaphylaxis	Polyethylene glycol
Moderna Vaccine	2 shots 28 days apart+	In use	94.1%	18+	Pain, swelling, redness at injection site, chills, tiredness, headaches, fever, anaphylaxis	Polysorbate, Polyethylene glycol
Johnson& Johnson Vaccine	1 shot	In use	66.3%	18+	Rare blood clot in women younger than 50, pain, swelling, redness at injection site, chills, tiredness, headaches, fever, anaphylaxis	Polysorbate

*** All vaccines should not be given until 90 days after monoclonal antibody administration.**

+ Patients that are moderately or severely immunocompromised should receive a third shot

VACCINE EFFICACY AGAINST VARIANT COVID-19 STRAINS

Vaccine	Delta Variant	Alpha Variant
Pfizer	**88%**	**93.7%**
Moderna	**-**	**-**
Johnson&Johnson	**-**	**-**

(-) There is not enough published information at this time.

PFIZER VACCINE

- BioNTech, Pfizer, and Fosun Pharma have developed a two-dose mRNA vaccine that has recently expanded to include people of 12 years old and up. They have also reported results stating that individuals who received the first dose experienced mostly mild to moderate side effects.
- 12/11/2020 -- FDA gave the Pfizer vaccine EUA in the United States.
- 08/12/2021 -- FDA announced that moderate to severely immunocompromised individuals should receive a third dose of the Pfizer vaccine a minimum of 28 days after the second dose was administered to produce a sufficient immune response.
  - A list of conditions that qualify for needing a third shot is on the CDC website
  - The FDA and CDC state that the timing of the third dose should be determined by physicians based on the timing of their patient's immunosuppressive therapy.
- Adverse effects of the vaccine have been mild to moderate, and start within 1-2 weeks after getting the vaccine, but should go away in a few days. Most common side effects reported include pain, swelling, and redness in the injection site and chills, tiredness, and headaches. Side effects such as fevers, chills, tiredness, and headaches are more common after the 2nd dose of the vaccine.
- The vaccine is reported by the NIH to be 95% effective in preventing symptomatic COVID-19.
- 04/01/2021 -- an analysis performed on 927 symptomatic COVID-19 cases found the vaccine to be 91.3% effective against COVID-19 from seven days to six months after the second dose. New data suggests the vaccine is 87-89.5% effective at preventing disease with the B.1.1.7/UK variant and 72.1-75% effective at preventing disease with the B.1.135/South African variant in people that were at least two weeks past their second dose. Overall, the vaccine is 100% effective at preventing severe, critical, or fatal disease cause by the UK and South African variants.
- A study is currently underway to test the efficacy of a third dose of the Pfizer vaccine as a booster shot.

- A study published by the New England Journal of Medicine found the Pfizer vaccine to be 88% effective against the delta variant and 93.7% effective against the alpha variant.
- In their latest executive report, the company explained that several individuals have waned immunity 8+ months after completed vaccination, warranting a booster. Currently, the booster is just a third shot identical to the first and second with the anticipation that circulating antibodies will be produced and increase protection of individuals. Current trials showed that the booster increases the amount of Delta variant antibodies fivefold in 18-to-55-year-olds and 11-fold in 65–85-year-olds. Studies began in August regarding an updated booster with the potential to confer added resistance against more novel strains. Boosters are on target to be distributed to the public as early as September 20th.

MODERNA VACCINE

- Moderna has developed a two-dose mRNA-based vaccine for individuals 18 years and older, and a phase 3 study determined the vaccine is 94.1% effective in preventing symptomatic COVID-19.
- 02/18/2020 -- FDA gave the Moderna vaccine EUA in the United States
- 08/12/2021 -- the FDA and CDC are recommending moderate to severely immunocompromised individuals should receive a third dose of the mRNA vaccine. The third dose should be given a minimum of 28 days after the second dose. Physicians should work with their patients to decide the best time for the third dosed based on their individual immunosuppressive treatment regimen. A full list of conditions that qualify for a third dose are located on the CDC website.
- Adverse effects have been mild to moderate and more common after the 2nd dose. Most common side effects reported include pain, swelling, and redness in the injection site, and chills, tiredness, and headaches. People who are allergic to polyethylene glycol or polysorbate should not get this vaccine
- A study performed by the CDC tracked front-line workers, first responders, and essential workers who had completed their second dose over 13 weeks found the vaccine to be 90% effective against protecting from COVID-19 in current conditions
- 06/29/2021 Moderna announced in a press release that their vaccine was protective against the delta variant based on studies they performed. The Moderna vaccine has been found to be protective against all the variant strains
- 09/01/21 -- Moderna announced submission of data to the FDA in support for its 50 mcg booster dose of their mRNA-1273 COVID-19 vaccine. Preliminary release of data showed that in n=344 participants, neutralizing antibody titers against SARS-CoV-2 significantly declined at 6 months from their second dose. Participants who received a booster dose demonstrated a 32-fold increased geometric mean titer for Beta variant, and 42.3-fold increased geometric mean titer for Gamma and Delta variants.
- 09/05/21 -- Moderna's data regarding boosters is lagging and will not meet the September 20th deadline set by the Biden Administration.

JOHNSON & JOHNSON VACCINE

- 02/27/2021 -- the FDA announced the EUA of the single-dose COVID-19 vaccine developed by Johnson&Johnson. The vaccine is recommended for people aged 18 years and older. The vaccine was 66.3% effective in clinical trials. People had most protection 2 weeks after getting the vaccine. This vaccine had high efficacy in preventing hospitalizations and death in people who did not get sick. This vaccine may provide protection against asymptomatic infection.
- 04/13/2021 -- The FDA and CDC have temporarily paused the use of Johnson&Johnson vaccines due to a small percentage of women receiving the vaccine developing severe and rare blood clots. The blood clot has been found in fifteen women and over 6.8 million doses of the vaccine have been given thus far. The blood clot occurred in women between the ages of 18 and 59. They reported that their symptoms began 6-15 days after vaccination

- 04/23/2021 -- The CDC and FDA lifted the pause on Johnson&Johnson vaccines. Now, women under the age of 50 must be notified of the potential risk for blood clots and be made aware of other COVID-19 vaccines available.
- There is currently conflicting data on the effectiveness of the J&J vaccine against the delta variant. A new study indicates that this vaccine is less effective than the others at protecting against the variant strain, however this data is not peer-reviewed nor published. However, peer-reviewed study showed that Johnson&Johnson demonstrated that the vaccine was as effective as the Pfizer vaccine against the delta variant. Several health officials have begun recommending a booster shot and advise that the most vulnerable populations are prioritized. Although there have been concerns over possibly needing a different vaccine to confer immunity with the new Delta variant, health officials do not recommend mixing vaccines due to the nature of the J&J vaccine being an adenovirus vector vaccine while Pfizer and Moderna are vector vaccines. There is currently no FDA approval regarding mixing vaccines.
- 09/02/21 -- J&J published a correspondence in NEJM to release interim phase 1/2a data about their Ad26.COV2.S vaccine. In n=20 participants who received either 1 or 2 doses of the J&J vaccine, compared to n=5 who received placebo, at 8 months after the single-shot regimen and 6 months after the two-shot regimen, participants who received vaccine demonstrated durable humoral and immune response.

COVID-19 VACCINES IN PHASE 3 US CLINICAL TRIALS

Vaccine	Number of Doses	FDA Status	Efficacy	Age	Side Effects	Allergies
Vaxzevria (AstraZeneca)	2 shots 4-12 weeks apart	Not in use	82%	18+	Vomiting, diarrhea, swelling, redness at the injection site and low levels of blood platelets occurred in less than 1 in 10 people.	Polysorbate
Novavax *	2 shots 1month apart	Not in use	- *	18+	- *	- *

***Novavax is currently still being studied.**

VAXZEVRIA (ASTRAZENECA) VACCINE

- AstraZeneca and the University of Oxford have developed a vaccine called ChAdOx1
- 10/23/2021 -- After halting global trials in September due to a volunteer who had developed transverse myelitis, the FDA authorized the restart of the trial
- Analysis of the phase III US trials demonstrated a 76% efficacy against symptomatic COVID-19 after the first dose and 82% efficacy after the second. It has been 100% effective against development of severe COVID-19 symptoms and hospitalizations. In participants 65 and older, the vaccine has been found to be 85% effective. The AstraZeneca vaccine has been found to produce a rare form of blood clot in a small percentage of those vaccinated

- 04/04/2021 -- there were 222 cases out of the 34 million vaccinated with this formula in the European Union and United Kingdom
- 04/14/2021 -- the Pharmacovigilance Risk Assessment Committee (PRAC) concluded that a causal relationship between vaccination with Vaxzevria and very rare cases of thrombosis together with thrombocytopenia, sometimes accompanied by bleeding, is plausible. Although rare, the cases of cerebral venous sinus thrombosis, splanchnic vein thrombosis and arterial thrombosis exceed what is observed in the general population. Most of these cases occurred 14 days after vaccination and mostly in women under 60 years of age. PRAC agreed that the product information for Vaxzevria should be updated with this assessment and specify thrombocytopenia as a new common side effect (occurring in less than 1 in 10 persons) and thrombosis in combination with thrombocytopenia as a new very rare side effect (occurring in less than 1 in 10,000 persons)
- June 2021 – The estimated risk of TTS from a single dose of the Astrazeneca vaccine was published. The age group with highest risk are <50 years old with 3.1 estimated cases per 100,000 first doses of Vaxzevria. All other age groups had lower estimated risk.
- A study published by the New England Journal of Medicine found the vaccine to be 67% effective against the delta variant and 74.5% effective against the alpha variant.

NOVAVAX VACCINE

- Novavax is a vaccine based on the genetic sequence of the SARS-CoV-2 and does not contain any live or inactivated virus. It was created using Novavax's nanoparticle technology and contains a patented adjuvant (Matrix-MTM) for immune boosting and neutralizing antibody stimulation, allowing a stronger immune response at a lower vaccine dose
- Nov 2020 -- Novavax started Phase 3 trials in adults 18 years and older in the United States and Mexico. The trial has also been opened at UT Health Antonio, and study participants will be followed for 2 years
- An analysis of the United Kingdom and South African trials showed the vaccine was effective in providing protection against variant strains. In the UK, the vaccine proved to be 96.4% effective against the original COVID-19 strain, 100% effective against the severe strain, and 86.3% against the UK variant. In South Africa, the vaccine in trial Phase 2b and has been found to be 100% protective against severe disease and 48.6% effective against the South African variant
- 06/14/21 -- Results from the phase 3 clinical trial (PREVENT-19) showed 90.4% efficacy of the Novavax vaccine in preventing symptomatic COVID-19 disease. Safety data showed the vaccine is generally well tolerated – primarily mild-moderate injection site tenderness, fatigue, headache lasting around 2 days

NOVOVAX INFLUENZA + COVID 19 COMBINATION VACCINE

- May 2021 -- Novavax announced that in the preclinical trials, the NanoFlu/NVX-CoV2373 combination vaccine demonstrated positive immune responses to both influenza and SARS-CoV-2

INTERNATIONAL VACCINE STUDIES

- The Murdoch Children's Research Institute is conducting a Phase 3 trial in Australia to see if the BCG vaccine partly protects against COVID-19.
- CanSinoBIO, the Gamaleya Research Institute, Bektop, Sinovac, Sinopharm, and the Wuhan Institute of Biological Products have developed vaccines that are approved for limited use in international countries. None are approved in the U.S. as of 7/25/21.