TREATMENT GUIDELINE FOR PATIENTS WITH COVID-19

This is a living document that will be updated as more data emerge.

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Table 1. Overview of Treatment Recommendations Based on Hospitalization and Severity of Disease

Not Hospitalized – Recommended Treatment	
• Supportive care • Consider monoclonal antibody if **within 10 days of symptom onset** and meet EUA criteria (see Table 2)	
Hospitalized	**Recommended Treatment**
No supplemental oxygen (or if on chronic oxygen therapy, not requiring an increase in baseline oxygen flow rate due to COVID-19)	• Supportive care • Monoclonal antibodies (only if admitted for reasons not related to COVID-19 and meet EUA eligibility criteria; restricted to ID physicians – see Table 2) • ***Consider*** convalescent plasma (restricted to ID physicians - see Table 2 for criteria for use) • Anticoagulation: refer to **COVID-19 Anticoagulation and Coagulopathy Management for Adults**
Low-flow supplemental oxygen (i.e., persistent SpO2 ≤ 94% on room air AND requiring supplemental oxygen)	• Remdesivir (restricted to ID physicians) for 5 days or until discharge, whichever comes first --PLUS-- • Dexamethasone 6 mg IV/PO daily for up to 10 days or until discharge, whichever comes first • ***Consider*** convalescent plasma if on ≤2L/min oxygen (restricted to ID physicians - see Table 2 for criteria for use) • Anticoagulation: refer to **COVID-19 Anticoagulation and Coagulopathy Management for Adults**
Non-invasive ventilation or high-flow oxygen devices	• Dexamethasone 6 mg IV/PO daily for up to 10 days or until discharge, whichever comes first (consider higher dose in select patients – refer to Table 2) --PLUS -- • ***Consider*** remdesivir (clinical benefit uncertain - restricted to ID physicians) for 5 days or until discharge, whichever comes first • ***Consider*** tocilizumab (restricted to ID physicians) • Anticoagulation: refer to **COVID-19 Anticoagulation and Coagulopathy Management for Adults**
Mechanical ventilation or ECMO	• Dexamethasone 6 mg IV/PO daily for up to 10 days or until discharge, whichever comes first (consider higher dose in select patients – refer to Table 2) • ***Consider*** tocilizumab (restricted to ID physicians) • Anticoagulation: refer to **COVID-19 Anticoagulation and Coagulopathy Management for Adults**

SUGGESTED LABORATORY MONITORING

Obtain at baseline and with any sudden decline in oxygenation status

- Complete blood count with diff: Leukopenia: 17-45%; Lymphopenia: 33-85%
- Comprehensive metabolic panel: LFTs (generally elevated)
- Lactate dehydrogenase (increased 27-75%)
- D-dimer (generally increased)
- Ferritin (generally increased)
- C-reactive protein (generally increased)
- Procalcitonin (refer to Table 3)

Table 2. Recommended Agents for Therapeutic Management of COVID-19

Monoclonal Antibodies for COVID-19 - *Prescriber must complete all EUA requirements*

Available Agents

- **Bamlanivimab** 700 mg IV once
- **Bamlanivimab** 700 mg IV plus **Etesevimab** 1400 mg IV x 1
- **Casirivimab** 1200 mg IV plus 1200 mg **Imdevimab** IV x 1

Inclusion

- Outpatient or an inpatient admitted for reasons not related to COVID-19
- Positive SARS-CoV-2 test (i.e., RT-PCR or antigen, not antibody test)
- Symptom onset within the last 10 days
- Patients with mild to moderate COVID-19 who are at high risk for progressing to severe COVID-19***** (see criteria below)

Exclusion

- <12 yo
- <40 kg
- Requiring supplemental oxygen (or if on chronic oxygen therapy, requiring an increase in baseline oxygen flow rate due to COVID-19)
- Received convalescent plasma

****High risk criteria for progressing to severe COVID-19 (must meet either adult or pediatric criteria below)***

Adult Criteria: ≥18 yo and ≥ 40 kg AND one of the following:

- Body mass index (BMI) ≥35
- Chronic kidney disease (CKD)
- Diabetes
- Immunosuppressive disease
- Currently receiving immunosuppressive treatment
- 65 years of age or older
- 55 years of age AND have
    - Cardiovascular disease, **OR**
    - Hypertension, **OR**
    - Chronic obstructive pulmonary disease/other chronic respiratory disease

Pediatric Criteria: 12 – 17 yo and ≥ 40 kg AND one of the following:

- BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm, **OR**
- Sickle cell disease, **OR**
- Congenital or acquired heart disease, **OR**
- Neurodevelopmental disorders, for example, cerebral palsy, **OR**
- A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), **OR**
- Asthma, reactive airway or other chronic respiratory disease that requires daily medication for control

Remdesivir (Restricted to Infectious Disease physicians. Use will be audited by the Antimicrobial Stewardship Team)

Inclusion

- Positive SARS-CoV-2 test (i.e., RT-PCR or antigen, not antibody test)
- Symptom onset within the last 14 days
- Persistent SpO2 ≤ 94% on room air and requiring supplemental oxygen or on non-invasive ventilation or high-flow oxygen devices

Exclusion

- Mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
- Reinfection with COVID-19 (positive SARS-CoV-2 test within 90 days of first positive SARS-CoV-2 test)
- Weight <3.5 kg
- Patients being transferred/awaiting transfer
- Less than 6 months life expectancy as determined by the attending physician or a consulting physician (*e.g.,* oncologist for patients with malignancy, FAST score 7C or more [or as assessed by geriatrics or palliative care] for dementia, etc)

Precautions

- eGFR<30 ml/min: the pharmacokinetics have not been evaluated in patients with eGRF <30 ml/min. The risk of toxicity in these patients is small and benefit of remdesivir likely outweighs this risk.
- ALT ≥ 5 x ULN at baseline: risk of hepatotoxicity in these patients is not known due to exclusion from clinical trials. Use of remdesivir should be based on potential risk versus benefit considerations.

FDA approved for the following patients: hospitalized adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization	EUA criteria (*prescriber must complete all EUA requirements for these patients)*: hospitalized pediatric patients 3.5 kg to <40 kg or pediatric patients <12 yo weight at least 3.5 kg. Please see below for additional requirements for healthcare providers for use in these patients.
Adult Dosing: 200 mg IV x 1 on day 1, then 100 mg IV daily for days 2 – 5 or until hospital discharge, whichever comes first. If patient progresses to requiring mechanical ventilation they should still complete the 5 day course.	**Pediatric Dosing*:** < 40 kg: 5 mg/kg IV load on day 1, then 2.5 mg/kg IV q24hr for days 2-5 ≥ 40 kg: 200 mg IV load on day 1, then 100 mg IV q24hr for days 2-5

Laboratory Monitoring

- Prior to initiation: Scr/BUN, hepatic function, prothrombin time
- During therapy: hepatic function (every 2-3 days or daily if ALT elevated), and Scr/BUN and prothrombin time should be monitored as clinically appropriate
    - Consider discontinuing if ALT >10 x ULN
    - Discontinue if ALT elevation accompanied by signs or symptoms of liver inflammation
- Pharmacists can order necessary labs listed above for patients receiving remdesivir

Infusion-related reactions (e.g., hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering): Slow infusion rate, with a maximum infusion time up to 120 minutes, to potentially prevent these signs and symptoms. If clinically significant infusion-related reactions occur, immediately discontinue & initiate appropriate treatment.

Remdesivir *(continued)*

Pregnancy and Nursing Mothers: Insufficient data to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Remdesivir demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals.

EUA Requirements for the Health Care Provider (applicable to pediatric patients 3.5 kg to <40 kg or pediatric patients <12 yo weight at least 3.5 kg)
Must provide copy of "Fact Sheet for Patients or parent/caregivers" prior to the patient receiving remdesivir, however, *"if providing this information will delay the administration of remdesivir to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as practicable after remdesivir is administered."*

1. Discuss the following information
    a. EUA does not mean FDA approved
    b. Patient or parent/caregiver can refuse
    c. Risks/benefits of remdesivir, availability of alternatives
2. Record in Epic that the patient/caregiver has been (use dotphrase .remdesivir):
    a. Given the Fact Sheet for Patients and Parents/Caregivers
    b. Informed that remdesivir is an unapproved drug that is authorized for use under EUA
    c. Informed of alternatives to receiving remdesivir
3. Required FDA Medwatch reporting
    a. Report any death or serious adverse event within 7 calendar days from the onset
    b. All medication errors
    c. FDA Medwatch: www.fda.gov/medwatch/report.htm
    d. Include "Remdesivir under EUA use" in top line of event description
        i. Serious Adverse Events are defined as: death from any cause while on therapy, life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly/birth defect, medical or surgical intervention to prevent death, life-threatening event, hospitalization, disability, or congenital anomaly
        ii. Provide copy of all FDA MedWatch forms to Gilead: Safety_fc@gilead.com

Steroids*

Recommended in adult patients with ***persistent*** SpO2 ≤ 94% on room air **AND** requiring supplemental oxygen (i.e., on low- or high-flow nasal oxygen, non-invasive or invasive mechanical ventilation, or ECMO):

- ***Preferred (non-pregnant adult patients):*** Dexamethasone 6 mg IV/PO q24h ***for up to 10 days (or until discharge if earlier)***
- ***Pregnant Patients:***
  - COVID-19: Methylprednisolone 40 mg IV/PO daily for up to 10 days (or until discharge if earlier)
  - COVID-19 and fetal lung maturity: Start with dexamethasone 6 mg IV/PO q12h **x 4 doses**, then methylprednisolone 40 mg IV/PO daily to complete a total of 10 days or until discharge (whichever comes first)
- Alternatives if dexamethasone is unavailable:
  - Methylprednisolone 40 mg IV q24h for up to 10 days (or until discharge if earlier)
  - Prednisone 40 mg PO q24h for up to 10 days (or until discharge if earlier
- For ***select*** patients on high-flow nasal oxygen, non-invasive or invasive mechanical ventilation, or ECMO ***(based on physician discretion):***
  - Consider high-dose steroids (maximum recommended dose dexamethasone 20mg/day or methylprednisolone 80mg/day):
    - Dexamethasone 20 mg IV/PO q24h x 5 days, then 10 mg IV/PO q24h x 5 days --OR--
    - Methylprednisolone 40 mg IV q12h x 5 days, then 40 mg IV q24h x 5 days
- **Monitor:**
  - Oxygenation status, CRP, ferritin, and LDH. If no improvement, rule out secondary bacterial infection.
  - Blood glucose in high risk individuals. Consider point-of-care blood glucose monitoring 4 times per day for 24-48 hours to monitor for steroid induced hyperglycemia, hyperglycemic crises, and new onset diabetes or for chronic diabetes management.
- For adult patients with refractory septic shock and COVID-19 the recommendation is to follow surviving sepsis guidelines with consideration for use with hydrocortisone 200 mg IV per day divided.
- Drug-drug interactions: The combination of dexamethasone and direct oral anticoagulants (DOACs: apixaban, rivaroxaban, dabigatran, edoxaban and betrixaban) ***should be avoided***. Dexamethasone is believed to be a combined P-glycoprotein and strong CYP 3A4 inducer. When used in combination with DOACs there is a potential for reduced DOAC drug concentration and increased risk of thrombosis.
- Stress ulcer prophylaxis: consider in patients also on therapeutic anticoagulation, mechanical ventilation, and/or patients with coagulopathy

Pediatric patients: Methylprednisolone IV (at an appropriate weight-based dose) may be initiated in pediatric ICU patients by the Pediatric Intensivist on a case-by-case basis. As literature evolves, recommendations and dosing in pediatric patients will be updated.

**for patients with a contraindication to steroids, consult Infectious Diseases to determine possible alternatives*

Convalescent Plasma (Restricted to Infectious Disease physicians - *Prescriber must complete all EUA requirements*)

Dosage: One unit of convalescent plasma (~200 mL)

- Redosing: additional convalescent plasma units based on prescribing physician's medical judgment and patient's clinical response
- Impaired cardiac function and heart failure: patients may require a smaller volume or more prolonged transfusion times

Inclusion

- Laboratory confirmation of SARS-CoV-2
- On room air or ≤ 2L/min supplemental oxygen
- Symptom onset within the last 7 days (except for patients with impaired humoral immunity, for which there is no duration of symptom cutoff*)

  *Impaired humoral immunity: Primary or acquired immunodeficiency (e.g., lymphoma, leukemia, tumors involving bone marrow, and patients receiving chemotherapy, HIV/AIDS [i.e., CD4 <200]), severe neutropenia (ANC <0.5), solid organ transplant, bone marrow transplant, multiple immunosuppressive medications

Exclusion

- Age < 18 years
- Requiring >2 L/min of oxygen supplementation
- Receipt of monoclonal antibody for treatment of COVID-19
- Contraindication to transfusion or history of prior life-threatening reactions to transfused blood products

Special Populations:

Pregnancy: Safety and effectiveness in pregnancy has not been evaluated. Discussion of risk versus benefit with the patient's care team, OB/GYN and Infectious Disease physicians should occur prior to administration in a pregnant patient

Side Effects: Overall low rates of serious adverse events. Potential side effects are similar to other blood products (*e.g.,* transfusion-transmitted infections [e.g. HIV, hepatitis B, hepatitis C], allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated cardiac overload (TACO), and hemolytic reactions).

EUA Requirements for Health Care Providers

1. Must maintain records and conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and must report fatalities related to transfusion to the FDA
2. Must provide recipients with the Fact Sheet for Patients/Caregivers and must communicate the following information to the recipients[†]:
   - FDA has authorized emergency use of COVID-19 convalescent plasma, which is not an FDA-approved biological product
   - The patient or caregiver has the option to accept or refuse administration of COVID-19 convalescent plasma
   - The significant known and potential risks and benefits of COVID-19 convalescent plasma and the extent to which such risks and benefits are unknown
   - Information on available alternative treatments and the risks and benefits of those alternatives.

[†]If providing this information will delay the administration of COVID-19 convalescent plasma to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as practicable after convalescent plasma is administered.

Tocilizumab (Restricted to Infectious Disease physicians)

Inclusion Criteria:

- Positive SARS-CoV-2 test (i.e., RT-PCR or antigen, not antibody test)
- Receiving high-flow oxygen or noninvasive ventilation or < 48h of mechanical ventilation

Exclusion Criteria:

- Mechanical ventilation > 48 hours
- ALT/AST > 5 x upper limit of normal
- Absolute neutrophil count < 500 cells/mm^3
- Platelet count < 50,000 cells/mm^3
- For solid organ transplant patients, ID prescriber can consult Dr. Dilip Samarapungavan regarding risk of administration (Pager: 248-992-8057)
- Hypersensitivity to tocilizumab or any excipients
- Patients with active pulmonary tuberculosis
- Strongly suspected bacterial or fungal infection
- Receiving baricitinib
- Previously received an IL-6 inhibitor during hospitalization or is on long-term therapy with an IL-6 inhibitor
- Patient has already received any dose of one or more of any form of tocilizumab, or sarilumab during this hospitalization or is on long-term therapy with any of these agents prior to this hospital admission

Adult Dosing:

8 mg/kg/dose (max: 800 mg; infused over 1 hour) x 1 dose

- For patients >40 kg, doses should be rounded as follows:
  - >90 kg: 800 mg
  - >65 to 90 kg: 600 mg
  - >40 to 65 kg: 400 mg
- A second dose of tocilizumab is not recommended due to increased risk of possible secondary infection and lack of proven benefit

Pediatric Dosing:

8 mg/kg/dose (max: 400 mg; infused over 1 hour) x 1 dose

Laboratory Monitoring: LFTs and CBC
Precaution: Not studied in patients CrCl < 30 mL/min; use caution in patients with diverticulitis (increased risk for GI perforation)
Pregnancy and Nursing Mothers: Discussion of risk versus benefit with the patient's care team, OB/GYN and Infectious Disease physicians should occur prior to administration in a pregnant patient
Adverse Reactions: Headache, hypertension, infusion reactions (rash, pruritus, nausea, hyper- or hypotension), LFT elevations, cytopenias, diarrhea, and allergic reaction (rare), and secondary bacterial and fungal infections

Table 3. Bacterial Co-infections and Other Treatment Considerations

Bacterial Co-Infections with COVID-19

Bacterial co-infections are uncommon in patients presenting with COVID-19 infection. A meta-analysis by Langford *et al* and Michigan cohort study (n=1705 patients) found only 3.5% of hospitalized patients had community-onset bacterial co-infection and risk was slightly higher in patients admitted directly to the ICU at 11%.[7,8] Secondary bacterial infections occurred in about 14% of COVID-19 patients.[7] A study by Zhou and colleagues found the median duration of fever to be 12 days (8-13 days) and cough persisted for 19 days in survivors.[1]

Procalcitonin*:* Low procalcitonin can be used to help rule-out bacterial co-infection (PCT <0.25), but PCT >0.25 ***should not be used as the only reason*** to initiate or continue antibiotic therapy. PCT >0.25 is common in patients with COVID-19 pneumonia, especially in patients with more severe disease (possibly due to systemic inflammation); therefore, it appears to be an unreliable marker of bacterial superinfection. Also, patients with CKD and AKI have falsely elevated PCT levels, and as such PCT is not reliable in these patients.[8,9]

Strongly Suspected or Confirmed MRSA pneumonia:

For patients with moderate to severe COVID-19 with suspected MRSA pneumonia:

- Anti-staphylococcal therapy is generally unnecessary, since concomitant bacterial infection appears to be uncommon
- For sites using AUC-guided dosing for vancomycin (i.e., RYO, TRY, GRP):
  - For any infection in which a vancomycin AUC goal of 400 – 600 is currently recommended switch to trough monitoring with a goal ~15 mg/L for patients with COVID-19
- If MRSA pneumonia is suspected: suggest oral linezolid instead of vancomycin to help decrease fluid volume and required blood draws
  - Check MRSA nasal swab and discontinue if negative
  - Check for drug-drug interactions prior to starting linezolid
  - Caution in patients with pre-existing myelosuppression
- For pediatric patients: linezolid is restricted to Infectious Diseases physicians
  - Infants & children < 12 years old: linezolid 10 mg/kg/dose (max: 600 mg/dose) PO every 8 hours
  - Children & adolescents ≥ 12 years: linezolid 600 mg PO every 12 hours or as recommended by Infectious Diseases

Current evidence does not support use of the agents below for treatment of hospitalized patients with COVID-19 (due to lack of efficacy and/or potential toxicity)

- Hydroxychloroquine +/- azithromycin
- Lopinavir/ritonavir (Kaletra)
- Oseltamivir
- Baloxavir
- Ribavirin
- Immune globulin (IVIG)
- Interferon
- Ivermectin *(current clinical and pharmacokinetic data do not support use; last reviewed 12.21.20)*
- Oral Vitamin C
- Colchicine *(insufficient data to determine if safe and effective for routine use for treatment of COVID-19)*

Other Treatment Considerations

ACEi/ARBs therapy: Patients chronically taking ACEi/ARBS should continue therapy. It is unclear if ACEi/ARBS will worsen or improve outcomes in patients with COVID-19.

Oral Vitamin C: Oral vitamin C does not achieve high enough concentrations in the serum for any potential therapeutic benefit due to saturable absorption. Also, oral vitamin C has the potential to cause harm, specifically AKI and/or kidney stones secondary to the accumulation of oxalate. Therefore, we do not recommend the use of oral vitamin C as adjuvant therapy for the treatment of COVID-19

Statins: Due to the lack of data, we do not recommend COVID-19 be the sole indication for statin therapy.

Other Treatment Considerations *(continued)*
Stress ulcer prophylaxis: consider in patients on steroids and therapeutic anticoagulation, mechanical ventilation, and/or patients with coagulopathy

Table 4. BH Investigational Studies

COVID-19 Investigational Studies at Beaumont Health			
Study Agent	**Location**	**Study Coordinator**	**Inclusion Criteria**
Naltrexone and Ketamine (SINK study)	RYO	Maureen Cooney, RN	1) ≤ 6L O_2 by nasal cannula randomized to low-dose naltrexone vs placebo, ketamine if O_2 requirements increase –OR-- 2) > 6L O_2 by nasal cannula enrolled as open label low-dose naltrexone & directly into the ketamine rescue group
Sirukumab	RYO	Lauren Brown, RN	≥ 4L oxygen with SpO2 <92% or PaO2/FiO2 ratio <300 or on mechanical ventilation < 72 hours
Convalescent Plasma (C3PO)	RYO	Blerina Pople Heather Grace	• One or more symptoms of COVID-19 illness and laboratory-confirmed SARS-CoV-2 infection. • Has at least one study defined risk factor for severe COVID-19 illness • Clinical team deems stable for outpatient management without supplemental oxygen • CP available at the site at the time of enrollment • Duration of symptoms ≤ 7 days at ED presentation
COVID-19 Vaccine	All sites	Maureen Cooney	≥ 18 yo, in good or stable health, at increased risk of getting COVID-19, and do not have a history of confirmed diagnosis of COVID-19. For more information visit: https://www.beaumont.org/covid-trial

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