COVID-19 ADULT TREATMENT GUIDANCE

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This is a living document and will be updated as new information merits

For questions or more information, please contact: *Helen Newland, PharmD* *Helen.Newland@bjc.org; cell: 913-526-5631*

PURPOSE

The purpose of this document is to provide guidance for the medication management of adult patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. For management of pediatric patients, please see St. Louis Children's Hospital COVID-19/MIS-C Treatment Recommendations.

Additional information can be found at the following resources:

- NIH COVID-19 Treatment Guidelines[1]
- IDSA Guidelines on the Treatment and Management of Patients with COVID-19[2]
- CDC Interim Clinical Guidance for Management of Patients with COVID-19[3]
- BJC COVID-19 Resources

MANAGEMENT

Consultation with clinical experts in the treatment of COVID-19 should be considered for management of critically ill patients, pediatric patients, pregnant/breastfeeding patients, and/or patients with risk factors for progression to severe COVID-19 illness*.[4, 5] [6]

Table 1. *Risk Factors for Severe Illness (CDC) [4]

Increasing age, especially over 65 years of age
Adults of any age with the following conditions are at increased risk for severe illness • Cancer • Chronic kidney disease • COPD • Down Syndrome • Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies • Immunocompromised state from solid organ transplant • Obesity (body mass index [BMI] ≥ 30 kg/m2) • Pregnancy • Sickle cell disease • Smoking • Type 2 diabetes mellitus
Adults of any age with the following conditions might be at an increased risk for severe illness • Asthma (moderate-to-severe) • Cerebrovascular disease • Cystic fibrosis • Hypertension • Immunocompromised state from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines • Neurologic conditions, such as dementia • Liver disease • Overweight (BMI > 25 kg/m2, but < 30 kg/m2) • Pulmonary fibrosis • Thalassemia • Type 1 diabetes mellitus

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

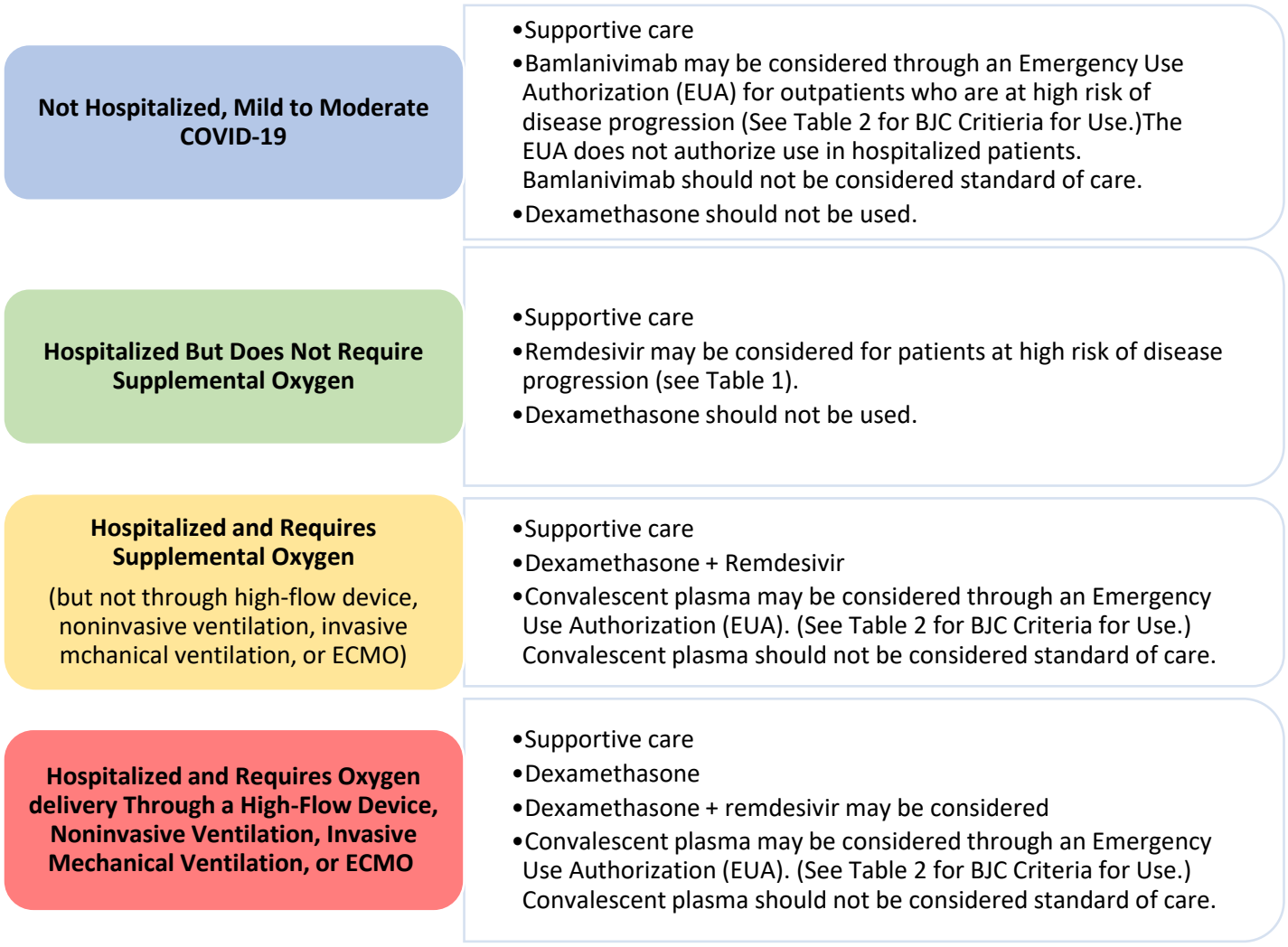

Table 2: Considerations for the management of COVID-19

Recommended as standard of care OR high-quality evidence supporting efficacy and safety [i.e., randomized, controlled trial(s)]

Supportive Care

- Appropriate management of respiratory failure, ARDS, sepsis, septic shock
- Unrelenting and high (>39°C) fevers are common in hospitalized COVID-19 patients.
- Antibiotics should only be used for confirmed or strong suspicion of a bacterial infection or sepsis. Antibiotics should be re-evaluated daily and if there is no evidence of bacterial infection, de-escalate or stop antibiotics.

Remdesivir (Veklury)[1, 2, 7-9]
 	
Appropriate Use Criteria:
 	
Hospitalized adult and pediatric patients (> 12 years old and weighing > 40 kg)
 	
Must meet all of the following:
• Symptomatic, laboratory-confirmed COVID-19
• Hospitalized for < 14 days
AND
Must meet at least 1 of the following:
• Severe and/or critical illness defined by:
  ○ Oxygen saturation (SpO2) of ≤ 94% on room air, or
  ○ Requiring supplemental oxygen, or
  ○ Requiring invasive mechanical ventilation, or
  ○ Requiring ECMO
• Symptomatic COVID-19 disease of any severity with one or more risk factors for progression to severe disease (see Table 1).
 	
Hospitalized pediatric patients weighing 3.5 kg to < 40 kg or less than 12 years of age weighing at least 3.5 kg
• Must meet Appropriate Use Criteria as listed above
• Remdesivir is available through the FDA's Emergency Use Authorization (EUA)
• See St. Louis Children's Hospital COVID-19/MIS-C Treatment Recommendations
	Adults:
	200mg IV on day 1, then 100mg IV q24h x 4 days, or hospital discharge, whichever comes first
	
	Pediatrics:
	≥ 40 kg
	200 mg IV on day 1, then 100 mg IV q24h x 4 days, or hospital discharge, whichever comes first
		• Antiviral that inhibits RNA-dependent RNA polymerase in SARS-CoV-2.
		• Multinational randomized controlled trial of remdesivir vs. placebo showed remdesivir significantly reduced time to recovery, 11 days vs. 15 days, respectively. Greatest benefit was seen in patients who required supplemental oxygen. No difference was seen in mechanically ventilated or ECMO patients.
		• Multinational study conducted by the World Health Organization that included 11,266 adults in 405 hospitals in 30 countries randomized to local standard of care vs. one of four different repurposed antivirals, 2750 were randomized to remdesivir. Compared to standard of care, there was no reduction in mortality, initiation of mechanical ventilation, or duration of hospitalization.
		• Multinational randomized open-label trial showed equivalent outcomes with 5 days of treatment compared with 10 days of treatment in non-mechanically ventilated patients.
		• Currently insufficient data on the optimal duration for mechanically ventilated, patients on ECMO, or patients who have not demonstrated clinical improvement after 5 days.
		• Pregnancy & Breastfeeding: There are no adequate and well-controlled studies in pregnant or breastfeeding women.
		• Pediatrics: Lyophilized powder should be used instead of the solution due to the higher amount of SBECD in the solution.
		• Renal Impairment: Although the manufacturer's labeling recommends against use in patients with eGFR < 30 mL/min, significant toxicity with a 5-day duration is unlikely.
		• Monitoring: eGFR, hepatic laboratory testing, prothrombin time

Dexamethasone[1, 2, 10-12]	**Adults:** 6 mg IV/PO daily for up to 10 days or until hospital discharge, whichever comes first.
	
	Pediatric: 0.15 mg/kg (maximum 6 mg) daily for up to 10 days or until hospital discharge, whichever comes first. See St. Louis Children's Hospital COVID-19/MIS-C Treatment Recommendations
		• Recommend using only in patients who are:
		  ○ Mechanically ventilated, or
		  ○ Require supplemental oxygen
		• Recommend against using in patients who do not require supplemental oxygen.
		• In a multicenter, randomized, open-label trial in hospitalized patients (RECOVERY), patients randomized to receive dexamethasone had a lower mortality than those who received standard of care. The benefit was seen in patients who required supplemental oxygen. No benefit was seen in patients who did not require supplemental oxygen.
		• A recent meta-analysis of seven randomized controlled trials found that administration of corticosteroids was associated with a lower 28-day mortality in critically ill patients with COVID-19.
		• Alternative steroid regimens have been evaluated with mixed results; however, the most robust clinical evidence remains with dexamethasone 6 mg IV/PO daily for up to 10 days.
		• Close monitoring for ADRs related to steroid use should be considered including hyperglycemia, electrolyte and fluid-balance abnormalities, secondary infections, psychiatric effects, and critical-illness related myopathy.

Recommended in the context of a clinical trial OR moderate-quality evidence suggests benefit and has lower potential for harm (i.e., well-designed retrospective, non-randomized studies)		

Convalescent Plasma[1, 2, 13]
• Convalescent plasma is available through the FDA's Emergency Use Authorization (EUA)
• **Convalescent plasma should not be considered standard of care for the treatment of patients with COVID-19**
  • Convalescent Plasma Fact Sheet for Health Care Providers
  • Convalescent Plasma Fact Sheet for Patients and Parents/Caregivers
  • Addendum to Fact Sheet for Patients and Parents/Caregivers (link to pdf in Epic order set and on BJC COVID-19 Website)
	• An FDA EUA was authorized based on limited data from the Mayo Clinic's Expanded Access Program which compared outcomes in patients who received plasma with low or high antibody titers (no placebo/control group). There was no difference in 7-day survival overall. In patients who were not intubated, 11% who received high-titer plasma died by day 7 compared to 14% of those who received low-titer plasma.
	• A recent randomized, double-blind, placebo-controlled trial of convalescent plasma with high antibody titers against SARS-CoV-2 in 160 patients > age 65 years with mild COVID-19 symptoms within 72 hours found 16% of patients receiving convalescent plasma had severe respiratory disease by day 15 compared with 31% of patients receiving placebo (Number Needed to Treat = 7.)
	• Available data suggest that serious adverse reactions are infrequent and consistent with the risks associated with plasma infusions for other indications.
	• Pregnancy & Breastfeeding: Safety and efficacy have not been evaluated.
	• Pediatrics: Safety and efficacy have not been evaluated. See St. Louis Children's Hospital COVID-19/MIS-C Treatment Recommendations

<table>
<tr><th colspan="2">Convalescent Plasma Inclusion Criteria (must meet all criteria)</th><th>Convalescent Plasma Exclusion Criteria (if meets any 1 criterion)</th></tr>
<tr><td colspan="2"><u>Adult (>/= 18 years)</u>
• Hospitalized patient with laboratory-confirmed SARS-CoV-2
• Respiratory disease with
  ○ New supplemental oxygen requirement to maintain SpO2 ≥ 93%
  ○ Acute or acute-on-chronic hypoxemic respiratory failure
• Primary team attending agrees that patient should be given COVID-19 convalescent plasma
• Informed blood transfusion consent provided by the patient or healthcare proxy
• FDA required
  ○ Convalescent Plasma Fact Sheet for Patients or Parents/Caregivers and
  ○ Addendum to Fact Sheet for Patients and Parents/Caregivers provided to patient or caregiver (link to pdf in Epic order set and on BJC COVID-19 Website)
  ○ Plasma will not be released unless the provider attests that both have been communicated to the patient/caregiver

<u>Pediatric (< 18 years)</u>
• Hospitalized patient with laboratory-confirmed SARS-CoV-2
• At least one of the following:
  ○ New supplemental oxygen requirement to maintain SpO2 ≥ 93%
  ○ Severe sepsis
  ○ Multiple organ failure
• Primary team attending agrees that patient should be given COVID-19 convalescent plasma
• Informed blood transfusion consent provided by the patient or healthcare proxy
• FDA required
  ○ Convalescent Plasma Fact Sheet for Patients or Parents/Caregivers and
  ○ Addendum to Fact Sheet for Patients and Parents/Caregivers provided to patient or caregiver (link to pdf in Epic order set and on BJC COVID-19 Website)
  ○ Plasma will not be released unless the provider attests that both have been communicated to the patient/caregiver</td><td><u>Adult (>/= 18 years)</u>
• Any reason for which the provider judges that COVID-19 convalescent plasma is not appropriate.
• > 10 days since symptoms began, or from first positive COVID-19 test if symptoms cannot be ascertained, unless immunocompromised. Immunocompromised patients will be considered beyond 10 days if requested by attending physician.
Consider the following exclusions:
• Patient has an underlying non-COVID Severely Life Limiting Comorbidity (commonly associated with survival of <1 year)
  • Severe Alzheimer's disease or related dementia
  • Cancer being treated with only palliative interventions (including palliative chemotherapy or radiation)
  • New York Heart Association Class IV heart failure plus evidence of frailty
  • Severe chronic lung disease plus evidence of frailty
  • Cirrhosis with MELD score ≥20, ineligible for transplant
  • End-stage renal disease plus frailty

<u>Pediatric (< 18 years)</u>
• Any reason for which the provider judges that COVID-19 convalescent plasma is not appropriate.
• > 10 days since symptoms began, or from first positive COVID-19 test if symptoms cannot be ascertained, unless immunocompromised. Immunocompromised patients will be considered beyond 10 days if requested by attending physician.</td></tr>
<tr><td>Bamlanivimab[14]
OUTPATIENT USE ONLY
• Bamlanivimab is available through the FDA's Emergency Use Authorization (EUA).
• Bamlanivimab should not be considered standard of care for the treatment of patients with COVID-19</td><td>Adults > 18 years old AND > 40 kg
700 mg IV x 1 over at least 60 minutes
• Observe for at least 1 hour after infusion complete
• Need immediate access to medications to treat severe infusion reaction such as anaphylaxis, and the ability to activate the</td><td>• Investigational recombinant neutralizing IgG1 monoclonal antibody (mAb), which binds to the spike protein of SARS-CoV-2, blocking entry into host cells.
• Interim analysis of randomized, double-blind, placebo-controlled trial (BLAZE-1) showed potential for decreased hospitalizations or emergency department visits among patients with mild to moderate COVID-19 who were at high risk for disease progression. [bamlanivimab pooled arm - 3% (4 of 136 patients) vs. placebo - 10% (7 of 69 patients), Number Needed to Treat = 14]</td></tr>
</table>

• See BJC COVID-19 Monoclonal Antibody Therapy website for more information • Bamlanivimab EUA Fact Sheet for Health Care Providers • Bamlanivimab EUA Fact Sheet for Patients, Parents, and Caregivers (English) • Bamlanivimab EUA Fact Sheet for Patients, Parents, and Caregivers (Spanish)	emergency medical system as necessary	• No benefit seen in hospitalized patients and may be associated with worse clinical outcomes in severe disease. • ADRs 2-4% nausea, diarrhea, dizziness, headache, pruritis, vomiting, potential for anaphylactic/infusion-related reactions. • Pregnancy & Breastfeeding: There are no data available in pregnant or breastfeeding women. Bamlanivimab may be considered if potential benefit outweighs potential risk. • Pediatrics: There are no data available regarding the use of bamlanivimab in children. At this time, bamlanivimab is restricted to adults in the BJC system. Rare exceptions may be considered by the Medical Officer on Duty in consultation with the Antimicrobial Stewardship Team.
Bamlanivimab Inclusion Criteria (must meet all criteria)		**Bamlanivimab Exclusion Criteria (if meets any 1 criterion)**

• Laboratory-confirmed COVID-19 (rapid antigen or PCR)
• Able to receive bamlanivimab within 10 days of symptom onset
• One or more symptoms consistent with COVID-19 (fever, cough, shortness of breath, fatigue, myalgia, headache, new loss of taste or smell, sore throat, congestion, runny nose, nausea or vomiting, diarrhea)
• Has at least one of the following high-risk conditions
  ○ Body mass index (BMI) of ≥ 35 kg/m2
  ○ Chronic kidney disease
  ○ Diabetes
  ○ Immunosuppressive disease
  ○ Currently receiving immunosuppressive treatment
  ○ ≥ 65 years of age
  ○ Age 55 to 64 years PLUS one of the following
  ▪ Cardiovascular disease
  ▪ Hypertension
  ▪ COPD/other chronic respiratory disease
		• Asymptomatic
		• Less than 18 years of age
		• Less than 40 kg
		• Hospitalized due to COVID-19
		• Requiring oxygen therapy due to COVID-19
		• Requiring increase in baseline oxygen due to COVID-19 in those on chronic oxygen therapy

Casirivimab + Imdevimab (REGN-COV2)[15] **OUTPATIENT USE ONLY** • Given the complex preparation and current error-prone labeling of casirivimab + imdevimab, **bamlanivimab will be the preferred mAb agent at BJC** unless bamlanivimab supply is depleted. • Casirivimab + Imdevimab is available through the FDA's Emergency Use Authorization (EUA). • **Casirivimab + Imdevimab should not be considered standard of care for the treatment of patients with COVID-19** • Neither bamlanivimab nor casirivimab + imdevimab is considered clinically superior over the other		• Interim analysis of randomized, double-blind, placebo-controlled trial showed potential for decreased hospitalizations or emergency department visits among patients with mild to moderate COVID-19 who were at high risk for disease progression. [casirivimab + imdevimab pooled arm – 2.6% (4 of 151 patients) vs. placebo - 9% (7 of 78 patients), Number Needed to Treat = 16] • Pediatrics: There are no data available regarding the use of casirivimab + imdevimab in children. At this time, casirivimab + imdevimab is restricted to adults in the BJC system. Rare exceptions may be considered by the Medical Officer on Duty in consultation with the Antimicrobial Stewardship Team.
Baricitinib (Olumiant)[16] • **Local Incident Command Center approval required** • Should only be given in combination with remdesivir and if dexamethasone cannot be given (extremely rare.)	• 4 mg PO daily for 14 days or until hospital discharge, whichever comes first	• Janus kinase (JAK) inhibitor that may prevent cellular immune activation and inflammation in COVID-19. Approved by FDA for severe rheumatoid arthritis. • A multinational, randomized, placebo-controlled trial (ACTT-2) in 1,033 hospitalized patients with COVID-19 pneumonia found median time to recovery was shorter in the baricitinib plus remdesivir group (7 days) than in the placebo group plus remdesivir group (8 days) in overall cohort.

		• ACTT-2 trial was done before dexamethasone established as standard of care with mortality benefit. • Should not be added on to remdesivir + dexamethasone (no data to support and potential for harm with potential additive risk of infection.)
Not recommended outside of a clinical trial **Low-quality (i.e., observational) or variable evidence to support use and has higher potential for harm**		
Tocilizumab (Actemra)[1, 2, 17-21] Tocilizumab is an established and proven agent required for several hematology/oncology and rheumatology indications. Stock of this drug has been and will continue to be sequestered to ensure the needs of these populations are met at BJC.	Not routinely recommended **Adults:** 8 mg/kg (max 800mg) IV x 1 dose **Pediatric:** <30 kg: 12 mg/kg IV x 1 ≥30 kg: 8 mg/kg IV x 1 (max 800 mg) If no response, may consider repeat dose in 8-12 hours, up to 3 total doses, but may not be available due to limited supply	• Tocilizumab has been proposed as a potential treatment for a suspected inflammatory syndrome caused by COVID-19 believed to be similar to cytokine release syndrome (CRS). Efficacy and safety of Tocilizumab for this syndrome has not been established. • A randomized, placebo-controlled trial (COVACTA) in 450 patients did not demonstrate improvement in clinical status, nor 4-week mortality. • A randomized, placebo-controlled trial in 389 patients found reduced likelihood of progression to mechanical ventilation or death (12% vs. 19%),but did not improve survival. • Additional randomized controlled trials have failed to demonstrate improvements in clinical outcomes of patients receiving tocilizumab for COVID-19. • Contraindications: ○ Active systemic bacterial or fungal infection ○ Pregnant or breastfeeding ○ AST/ALT 10 x upper limit of normal ○ Neutropenia (ANC < 500 cells/mm3) ○ Thrombocytopenia (<50,000 cells/mm3) ○ Note: if treating physician thinks lab abnormalities are due to COVID-19, then these may not necessarily be exclusionary • Serious adverse events include: ○ Secondary infections ○ Gastrointestinal perforation ○ Anemia ○ Hepatitis ○ Infusion reaction ○ Neutropenia • Half-life 11-17 days
Inhaled Prostanoids[22]	Not routinely recommended While there is insufficient data to provide recommendations specific to COVID-19, patients with ARDS may benefit from inhaled prostanoids. Please consult Critical Care for guidance	• To date, no studies have evaluated use in COVID-19 patients. • A nationwide shortage of available agents exists • Data in patients with non-COVID ARDS indicate inhaled prostanoids may reduce mean pulmonary artery pressure and improve oxygenation; however, data demonstrating clinical benefit are lacking. • Inhaled prostanoids are aerosolized for administration and require filter changes that increase potential exposure of particles within the ventilator circuit to the ambient environment.
Ivermectin[1]	Not recommended outside of a clinical trial	• Ivermectin is an antiparasitic drug being evaluated as a potential treatment for COVID-19 due to *in vitro* studies suggesting it may have antiviral and anti-inflammatory properties. • Although *in vitro* data suggests ivermectin may inhibit SARS-CoV-2 in cell cultures, pharmacokinetic and

		pharmacodynamic studies suggest ivermectin doses up to 100-fold higher than those approved for humans would be required to achieve the concentrations necessary to duplicate the drug's antiviral efficacy *in vitro*. • Most currently available clinical studies have incomplete information and significant methodological limitations such as small sample size, various doses and schedules of ivermectin, open-label in which neither participants nor investigators were blinded to treatment arms, various concomitant medications such as corticosteroids, and poorly defined severity and outcome measures. • Definitive conclusions cannot be drawn about the clinical efficacy or safety with currently available data.
Do not use (therapies with evidence of no benefit and/or potential for harm)[1, 2]		
Hydroxychloroquine (Plaquenil)[23-27]	Not recommended	Multiple randomized, double-blind, placebo-controlled trials have shown no evidence of benefit for post-exposure prophylaxis, nor treatment across the spectrum of disease severity. • Reports have documented serious dysrhythmias in patients with COVID-19 • Recommend telemetry or baseline EKG with regular monitoring, as QTc prolongation has been observed • Terminal half-life is 1-2 months • ADRs: bone marrow suppression, hypoglycemia, retinal toxicity
Azithromycin	Not recommended	• Has been studied only in combination with hydroxychloroquine, with no evidence of benefit in multiple studies. • Recommend telemetry or baseline EKG with regular monitoring as QTc prolongation has been observed.
Neuraminidase Inhibitors (oseltamivir, zanamavir, peramivir) **Baloxavir**	Not recommended	• Neuraminidase inhibitors are NOT recommended for treatment of COVID-19 as coronaviruses have not been shown to utilize neuraminidase for replication. • No data to support use of baloxavir. • Should only be utilized with influenza co-infection.
Other therapies **Lopinavir/ritonavir (Kaletra)** **Vitamin C** **Vitamin D** **Zinc** **Sarilumab, siltuximab** **Oral Ribavirin**	Not recommended	• Studies showing lack of clinical efficacy, or insufficient data to support use.

APPENDIX

Convalescent Plasma Emergency Use Authorization Requirements

- Convalescent Plasma Fact Sheet for Health Care Providers
- Convalescent Plasma Fact Sheet for Patients/Caregivers
- Convalescent Plasma Addendum to the Fact Sheet

Bamlanivimab

- BJC COVID-19 Monoclonal Antibody Therapy website
- Bamlanivimab EUA Fact Sheet for Health Care Providers
- Bamlanivimab EUA Fact Sheet for Patients, Parents, and Caregivers (English)
- Bamlanivimab EUA Fact Sheet for Patients, Parents, and Caregivers (Spanish)

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